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TRICUSPID INCOMPETENCE AND RIGHT VENTRICULAR OUTPUT IN CONGESTIVE HEART FAILURE

BY

PAUL KORNER* AND JOHN SHILLINGFORD†

From the Department of Medicine, Postgraduate Medical School, Hammersmith

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Studies of the right atrial pressure and flow curves in patients with cardiac failure show that with a venous pressure of more than 8 mm. Hg, increasing amounts of functional tricuspid regurgitation may occur (Muller and Shillingford, 1954; Korner and Shillingford, 1954). If the forward flow is maintained, backflow through the valve will add a variable amount to the right ventricular stroke volume. Until recently the amount of increased stroke volume caused by valvular incompetence could only be inferred from right atrial pressure curves and necropsy observations. With the development of the dye dilution technique for the quantitative estimation of regurgitant flow (Korner and Shillingford, 1955) it has now been possible to gain further knowledge of the effect of valvular incompetence on the cardiac output and its relation to heart failure.

The purpose of this paper is to correlate the quantitative estimates of valvular regurgitation with the clinical and necropsy findings in a group of patients with tricuspid incompetence and to discuss these results in relation to the performance of the right ventricle in congestive heart failure.

METHODS

Fourteen patients were studied; ten had rheumatic heart disease, two hypertensive heart disease, one cor pulmonale, and one amyloid disease of the heart. In all the jugular venous pressure was raised to above a mean of 10 mm. Hg measured from a reference point 5 cm. below the sternal angle. The phlebograms all showed evidence of a positive systolic wave with obliteration of the *X* descent. Cardiac catheterization was carried out in six patients using a Statham strain gauge with a direct current amplifier for the measurement of intracardiac pressures; the mean right atrial pressure in these patients varied between 11 and 26 mm. Hg and the tracings all showed a positive systolic pulsation. Dye dilution curves were made in all cases by the technique previously described (Korner and Shillingford, 1955).

Routine examination was made on the hearts of six patients who came to necropsy; in three patients additional information was obtained by inserting a tube into the right ventricle via the cut pulmonary artery and perfusing water through the tricuspid valve with the whole heart under water. The behaviour of the valve leaflets and the aperture of reflux were then observed and photographed through the opened right atrium. Twenty control hearts from patients without evidence of heart disease were subjected to this test at autopsy.

RESULTS

The typical dye dilution curves obtained from a control subject and a patient with valvular incompetence are shown in Fig. 1. The effect of added valvular incompetence for a given cardiac output and volume between the point of injection and sampling site is to shorten the appearance time, decrease the maximum concentration, and prolong the rate of fall of the descending limb of the curve. The actual regurgitant flow was computed from the change in the shape of the curve.

Fig. 2 shows the total right ventricular output and the amounts of regurgitant flow and forward

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† Member of the Medical Research Council Scientific Staff.

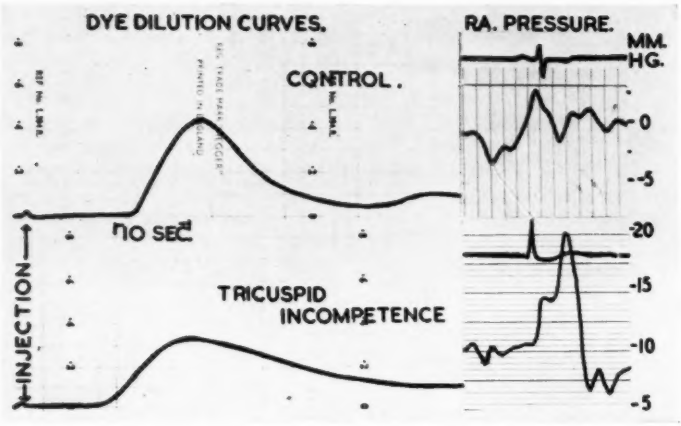

FIG. 1.—Dye dilution curves from a patient without valvular incompetence (above) and from one with tricuspid regurgitation (below). Corresponding right atrial pressure curves are shown alongside.

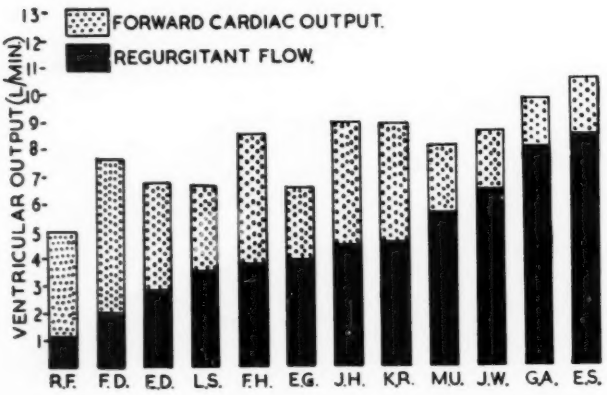

FIG. 2.—Total right ventricular output, showing the proportion of forward and regurgitant flows in twelve patients in congestive cardiac failure with tricuspid incompetence.

output in litres a minute in twelve of the patients, all of whom were in varying degrees of heart failure. The black columns represent the regurgitant flow from the right ventricle which varied between 1·2 and 8·2 litres a minute. The dotted columns represent the forward cardiac output from the right ventricle which varied between 5 and 2·1 litres a minute. The total right ventricular output, being the sum of regurgitant and forward flow, varied between 5·2 and 10 litres a minute. Although these patients were in congestive failure with, in most cases, a low forward cardiac output, the right ventricular output remained comparatively high and did not fall below 5·2 litres a minute. The average right ventricular stroke output was about 100 ml. and varied between 74 and 173 ml. As the regurgitant flow increased the forward flow tended to decrease and in cases where the latter was as low as 2·1 litres a minute the backflow reached about 8 litres a minute.

minute. In this case exercise did not significantly change the forward cardiac output although the

The Effect of Rest and Exercise. The effect of exercise and rest in two patients with congestive heart failure was studied. Both had rheumatic heart disease with mitral stenosis. Fig. 3 shows the change in the distribution of right ventricular output on rest and exercise in these patients. In the first (K.F.) the venous pressure, cardiac output, and regurgitant flow were measured when the

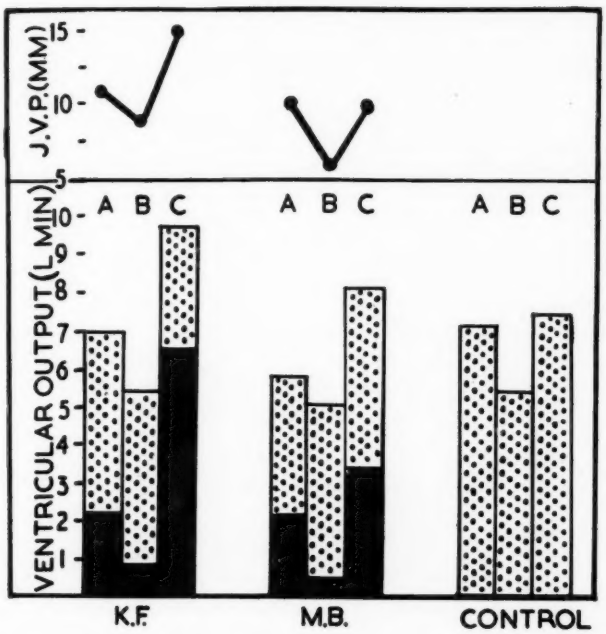

FIG. 3.—The effect of rest and exercise on the right ventricular forward and regurgitant flows on two patients compared with a subject not in cardiac failure. (A) Output soon after patient was placed on examination couch. (B) After 20 minutes rest. (C) After two minutes mild exercise.

patient was first placed on the examining couch. The mean jugular venous pressure was 11 mm., the forward cardiac output was 4·8 litres a minute, and the regurgitant flow 2·2 litres a minute, with a total right ventricular output of 7 litres a minute. After the patient had rested quietly for twenty minutes the venous pressure had fallen to 8 mm., the forward cardiac output was 4·5, and the regurgitant flow was 0·9, with a total right ventricular output of 5·4 litres a minute. After two minutes exercise by gentle movement of the legs, the venous pressure rose to 15 mm., the forward cardiac output fell to 3·2, and the regurgitant flow rose to 6·7 litres a minute. It will be noted that the forward output actually fell on exercise, although the total right ventricular output rose considerably.

The second (M.B.) on the first test showed a mean jugular venous pressure of 10 mm. Hg, a forward cardiac output of 3·7, a regurgitant flow of 2·1, and a total right ventricular output of 5·8 litres a minute. After the patient had rested quietly for twenty minutes further observations showed that the forward cardiac output had risen to 4·5, and the regurgitant flow was 0·5, with a total right ventricular output of 5 litres a minute. After two minutes gentle exercise the forward cardiac output was 4·6, the regurgitant flow 3·5, and the total right ventricular output 8·1 litres a

minute. In this case exercise did not significantly change the forward cardiac output although the right ventricular output was greatly increased.

Clinical Observations. The typical murmur of tricuspid incompetence (Muller and Shillingford, 1954) was heard in all cases (Fig. 4) but no correlation between the intensity of the murmur and the volume of backflow was attempted in this study. Three of the patients with an abnormally

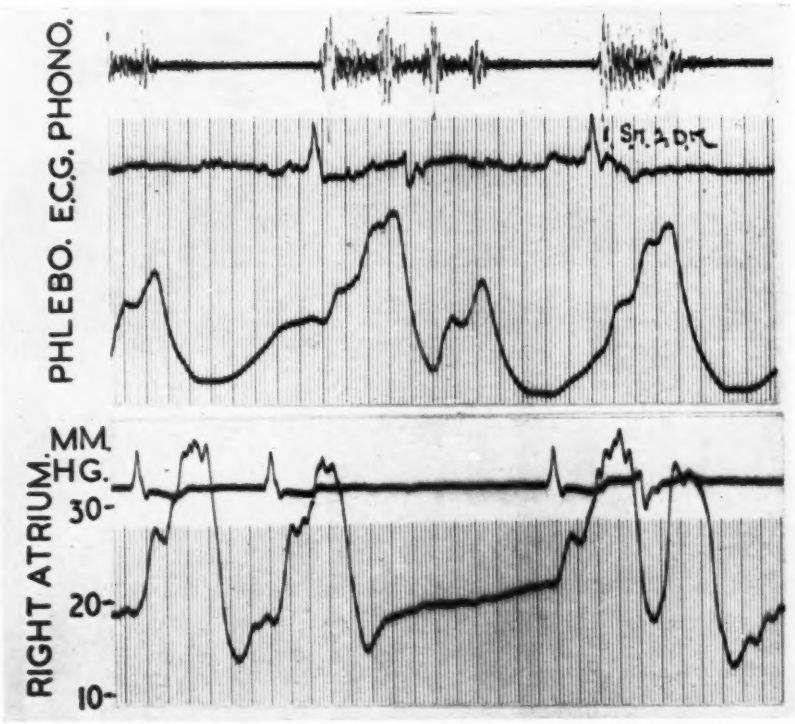

FIG. 4.—Phonocardiogram, phlebogram, and right atrial pressure pulse from patient J. H. (see text).

low forward cardiac output showed great right ventricular pulsation; this could be explained on the high right ventricular stroke output due to the addition of the tricuspid regurgitation. Systolic expansion of the liver appeared to be the physical sign most closely correlated with the volume of regurgitant flow; in no case where the regurgitant flow was below 3·5 litres a minute was there general agreement that liver pulsation could be felt; with backflows above this figure liver pulsation was palpable in the majority of patients. It is not difficult to appreciate that a regurgitant stroke output of 40 to 50 ml. or less could be readily taken up in the right atrium and great veins and not be readily felt as pulsation of the liver.

There was no simple relationship between the amount of regurgitant flow and the venous pressure. Fig. 5 shows the right atrial pressure plotted against regurgitant flow in litres a minute and also against right ventricular stroke output in six patients where accurate measurement of the right atrial pulse pressure was made at cardiac catheterization. The lack of relationship is not surprising as the right atrial pressure is determined not only by the backflow but by the volume elasticity relationships of the venous system. Other factors of importance in the elevation of the

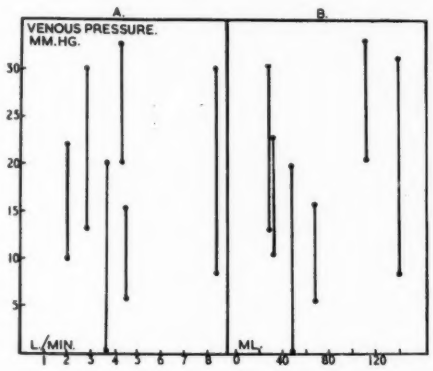

FIG. 5.—Relation of venous pressure (systolic and end-diastolic) to backflow. ((A) litres/min.; (B) ml./beat) in six cases of tricuspid incompetence.

central venous pressure probably include blood volume expansion, venous constriction, and increase in forward flow (Landis and Hortenstine, 1950). At the same time the relationship may not be the same in functional as in organic tricuspid incompetence.

A positive systolic wave of the jugular venous pulse was recorded in all the patients. When the pulse rate was slow, it was easy to recognize this pulsation by direct observation, but in cases with tachycardia and a corresponding lower stroke output the study of a jugular phlebogram was necessary to confirm the presence of a positive systolic wave.

Post-mortem Findings. Six patients came to necropsy; three of the hearts were studied in the routine way, while in the others the valves were perfused as previously described. A series of twenty control hearts showed the tricuspid valve to close competently to this test (Fig. 6B). Two of the cases subjected to this test showed organic disease of the valves with partial fusion of the cusps with an incompetent orifice of an average diameter of 2·5 cm. in each case; the other case was one of amyloid disease with dilatation of the valve ring and an incompetent orifice of 2·0 cm. diameter. All the cases were reported as showing dilatation of the right ventricular cavity and the tricuspid valve ring.

The pulmonary outflow tract and pulmonary valve from a normal heart are shown in Fig. 6A, with photographs of the tricuspid valve taken at the same magnification. It will be seen that the orifice of the incompetent tricuspid valve approached in size that of the pulmonary valve, adding further support to the hæmodynamic observations that the regurgitant flow may be as great or greater than the forward flow in patients with congestive heart failure and tricuspid incompetence. This regurgitant flow may be greater than the forward flow even if the orifices are of the same size, as in most cases the right atrial pressure is lower than the pulmonary arterial pressure.

Examples of two cases, one with organic and the other with functional tricuspid incompetence, are given below.

(1). *Clerk, aged 36 years.* Rheumatic fever at the age of 9 and 16; breathless on exertion after second attack. First seen at hospital at age of 32 with increasing breathlessness and upper abdominal discomfort. Slow auricular fibrillation. Jugular venous pressure 6 cm. above sternal angle with positive systolic pulsation. Cardiac enlargement to the right of the sternum. Apex beat 15 cm. to left of midline in the sixth interspace. Systolic and mid-diastolic murmurs at apex. Systolic murmur at aortic area and at lower end and to the right of the sternum. Liver enlarged three fingers' breadths with positive systolic pulsation. X-ray of heart showed enlargement of left atrium and right ventricle. E.C., right ventricular preponderance. Given digitalis with improvement. Last admission aged 36. Increasing congestive heart failure with œdema and ascites. Auscultation as before but with increase in the intensity of the tricuspid murmur and pulmonary second sound. Liver four fingers' breadths below costal margin with systolic pulsation. Right atrial pressure 35/20 (mean 26) mm. Hg. Total right ventricular output 8·9 litres a minute (forward flow, 4·5 litres a minute; regurgitant flow, 4·4 litres a minute).

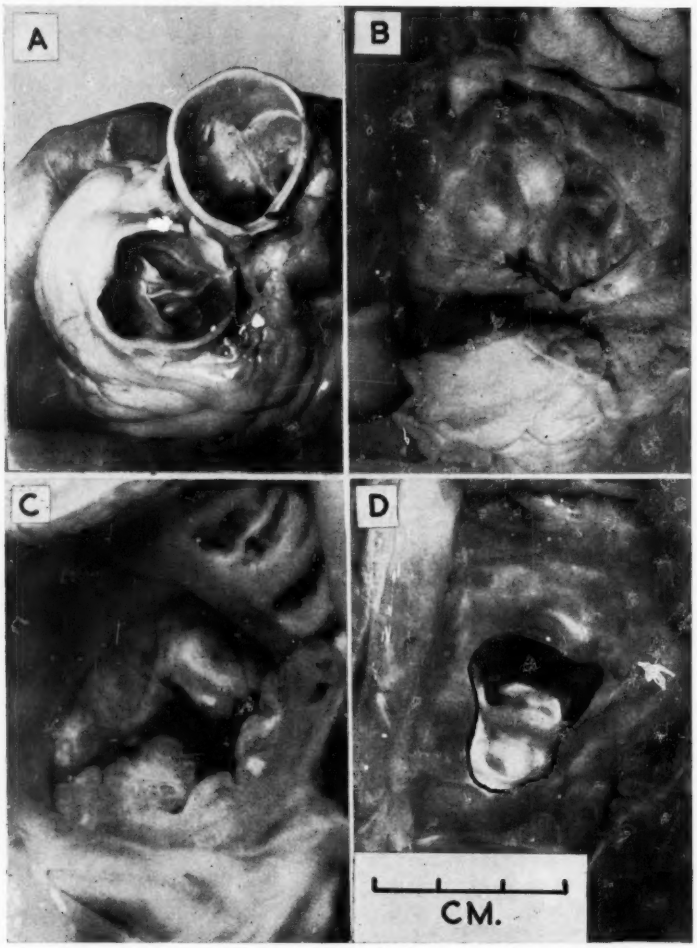

FIG. 6.—Necropsy photographs of the tricuspid valves during retrograde perfusion of the right ventricle. (A) Normal pulmonary valve. (B) Normal tricuspid valve. (C) Functional incompetence in a case of amyloid heart disease. Forward output 2·8, regurgitant flow 3·8 litres a minute. (D) Organic incompetence following fusion of the valves in a case of rheumatic heart disease. Forward output 4·5, regurgitant flow 4·4 litres a minute.

Necropsy. Heart 770 g. Left ventricle moderate hypertrophy and dilatation. Left atrium great dilatation and hypertrophy. Right ventricle great hypertrophy and dilatation. Mitral valve; button-hole stenosis admitting the tip of the index finger; chordæ tendineæ shortened, thickened, and fibrosed with calcified edges. Aortic valve, slight fusion of valve cusps. Tricuspid valve, fusion of cusps combined with dilatation of valve ring giving an incompetent orifice of 2·5 cm. diameter.

(2). *Housewife, aged 56 years*. Fifteen months chest pain on exertion, increasing breathlessness; six months discomfort in upper abdomen, occasional vomiting; six weeks œdema of legs and increasing dyspnœa.

O.E. Orthopnœa, œdema of legs and sacrum. Jugular venous pressure 10 cm. above sternal angle with positive systolic wave. Pulse rate 120 a minute, regular; B.P. 130/80. Apex beat in anterior axillary line in sixth interspace. Triple rhythm at apex and systolic murmur at lower end and to the right of the

sternum. Small right pleural effusion. Liver four fingers' breadths below costal margin, firm and smooth. X-ray of heart, moderate enlargement with prominent pulmonary artery. Pulmonary artery pressure, 40/28; right ventricular pressure, 40/5; right atrial pressure 30/15 mm. Hg. Total right ventricular output 6·6 litres a minute (forward flow 2·8, and regurgitant flow 3·8 litres a minute).

Necropsy. Heart 495 g. Moderate hypertrophy and dilatation of right atrium and right ventricle. Dilatation and resultant incompetence of tricuspid valve with incompetent orifice about 2·0 cm. diameter. Left ventricle hypertrophied, but not dilated. No coronary artery narrowing. Myocardium hypertrophied, pale, and glassy, with firm cut edge; strongly positive for amyloid reaction.

Discussion

Previous work has shown that in congestive heart failure a grossly raised venous pressure is usually accompanied by functional tricuspid regurgitation. The development of the dye dilution method (Korner and Shillingford, 1955) has enabled a quantitative estimate of the amount of regurgitation to be made. The results show that the average total right ventricular output at rest in patients with congestive heart failure and tricuspid incompetence is about 50 per cent higher than in normal resting subjects. There appeared to be an inverse relationship between the forward output and regurgitant flow, so that when the forward output was abnormally low the regurgitant flow was high. In the group studied, although the forward and regurgitant flow varied within wide limits between the patients, the total right ventricular output was relatively fixed. The effect of mild exercise on such patients was to increase the total ventricular output slightly, although the forward cardiac output might remain the same or even fall at the expense of increased regurgitant flow. This correlates with previous work where exercise has been shown to increase the mean right atrial pressure, the right atrial pulse pressure, the intensity of the systolic murmur, and the backflow in the atrium as measured by differential manometry (Muller and Shillingford, 1954; 1955). This alteration in the distribution of blood flow may help to explain the phenomenon of " fixed cardiac output " seen in cases of mitral stenosis and heart failure (Hickam and Cargill, 1948; Donald *et al.*, 1954).

The regurgitant backflow is regulated not only by the relative sizes of the orifices of the incompetent tricuspid valve and pulmonary outflow tract, but also by the pressure gradients between the right atrium, right ventricle, and pulmonary artery. For example, in one patient with functional tricuspid incompetence, where the regurgitant flow was a little less than the forward flow and the mean pulmonary arterial pressure twice that of the mean right atrial pressure, the diameter of the perfused incompetent valve at necropsy was about half that of the pulmonary outflow tract.

While exercise reduced the efficiency of right ventricular performance owing to the increased backflow, our results perhaps indicate that the improvement following rest and possibly venesection or digitalis (McMichael, 1950) could be the result of a diminution in the regurgitant flow.

Summary

Quantitative estimates of the amount of backflow through incompetent tricuspid valves have been correlated with the clinical and necropsy findings in fourteen patients in congestive failure.

When functional tricuspid incompetence develops in congestive failure the right ventricular output remains high in spite of a low forward cardiac output, because of the large regurgitant flow.

Exercise may increase the regurgitant flow at the expense of forward cardiac output. Rest has the opposite effect.

The regurgitant flow is thought to be important in maintaining a low fixed forward cardiac output in some cases of congestive cardiac failure.

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DIAGNOSIS OF CONGENITAL ANEURYSM OF THE VENTRICULAR SEPTUM DURING LIFE

BY

ISRAEL STEINBERG *

From the Departments of Medicine and Radiology, The New York Hospital, Cornell Medical Centre

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Aneurysms of the membranous portion of the ventricular septum are uncommon and there is general agreement that they are of congenital origin. These aneurysms may occur alone or with other cardiovascular anomalies. They are usually incidental findings at autopsy and seldom produce clinical manifestations. However, there are two reports of serious cardiac arrhythmias of many years duration that were attributed to the presence of septal aneurysms (Rogers *et al.*, 1952; and Clark and White, 1952).

The demonstration of a localized bulge of the left ventricular septum in a patient studied by angiocardiography is herein reported. Even though autopsy confirmation of a ventricular septal aneurysm is lacking, the distinctive features of the angiocardiogram strongly favour such a diagnosis. Further evidence for this conclusion is provided by comparison with a membranous ventricular septal aneurysm recently noted as an incidental finding at autopsy. The purpose of this report is to describe the angiocardiographic appearance of a suspected ventricular septal aneurysm and to propose criteria for the diagnosis of such aneurysms during life.

Case Report

A 60-year-old white housewife has been observed in the clinic and hospital for nearly five years. Cystitis was found on her first visit during 1950 and treated successfully. Subsequently she complained of mild dyspnœa and a routine chest roentgenogram revealed infiltration in the first right anterior interspace and an increase in the right hilar shadows. The heart appeared to be somewhat enlarged (Fig. 1A). Increased pulsation of the right descending pulmonary arterial branches was noted on fluoroscopic examination and an angiocardiogram was requested. Angiocardiography was normal except for a localized bulge to the right of the ventricular septum (Fig. 2).

During the five years under observation, the patient has had many complaints consisting of epigastric pain and discomfort. Studies, of the biliary, gastro-intestinal, and urinary systems revealed no abnormalities. The blood pressure was normal, 130/80. Standard, præcordial and vector electrocardiograms were normal except for left axis deviation and a P–R II of 0·21 sec. The heart examination was normal; no murmurs were elicited; the rhythm was normal sinus. Studies of the blood including the serologic test for syphilis were also normal. Tuberculin skin tests in all dilutions were negative. Biopsy of two skin papules failed to show sarcoidosis and no cervical, axillary, or inguinal masses have appeared. Roentgenograms of the chest during the five years have shown no change in appearance of the lungs, heart, or hilar structures.

Discussion

The embryological development of the membranous ventricular septum has been reviewed by Lev and Saphir (1936, 1938) and Rogers *et al.* (1952). The membranous ventricular septum is in part derived from endocardial cushion tissue and is intimately related to the closure of the atrioventricular canal. The closure is concerned with the union of tissues from the dorsal and ventral endocardial cushion systems, the primary interatrial septum, and the muscular interventricular

* Aided by a Grant-in-Aid from the American Cancer Society and the Mallinckrodt Chemical Works.

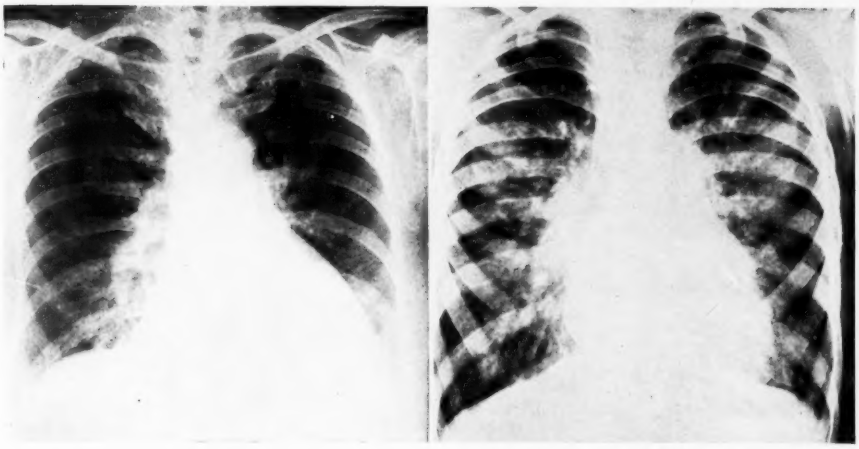

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FIG. 1.—(A) Teleradiogram from a woman, aged 60, showing slight increase in the size of the heart and prominence of the descending right pulmonary arterial branches. There is also minor right infraclavicular pulmonary infiltration. (B) Teleradiogram from an 8-year-old boy who died of bronchiectasis, bronchopneumonia, pulmonary emphysema, and cor pulmonale associated with fibrocystic disease of the pancreas. Note the enlarged heart, prominent pulmonary artery, and diffuse pulmonary fibrosis.

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About 80 cases of congenital aneurysm of the membranous ventricular septum have been reported. Lev and Saphir (1938) recorded 70 previously reported cases and added two new ones. Castoldi (1942), Leckert and Sternberg (1950), Vanecek (1950), Schlicter *et al.* (1954), Kjellberg *et al.* (1955), and Clark and White (1952) added a case; while Rogers *et al.* (1952), added two new ones. As for incidence, Rae (1936) noted that four membranous ventricular septal aneurysms were found in 3000 autopsies; on the other hand, only two were found in a total of 16,000 autopsies in this institution.

Fig. 3 is an autopsy specimen, showing an aneurysm of the membranous portion of the ventricular septum—an incidental finding in an eight-year-old boy. Death was due to bronchiectasis, broncho-pneumonia, pulmonary emphysema, and chronic cor pulmonale that resulted from long-standing pulmonary disease associated with fibrocystic disease of the pancreas (Fig. 1B). The aneurysm consisted of a one-cm. pouch which bulged from the membranous part of the interventricular septum into the right ventricle and was attached to a tricuspid valve leaflet. The heart weighed 180 g. (expected weight 110 g.). The right atrium and ventricle were much dilated; the right ventricle was hypertrophied and measured 8 mm. The pulmonary artery was conspicuously dilated. The left atrium and ventricle were normal; the left ventricle wall measured 8 mm. No communication between the ventricles was noted and the fossa ovalis was closed. All the valves were thin, smooth, and intact, and had normal measurements; the coronary arteries contained no lesions.

Two years before his death he had been admitted in severe congestive heart failure, due to cor pulmonale secondary to pulmonary fibrosis, which responded to digitalis and organic mercurial

DIAGNOSIS OF CONGENITAL ANEURYSM OF THE VENTRICULAR SEPTUM DURING LIFE

BY

ISRAEL STEINBERG *

From the Departments of Medicine and Radiology, The New York Hospital, Cornell Medical Centre

Received December 6, 1955

Aneurysms of the membranous portion of the ventricular septum are uncommon and there is general agreement that they are of congenital origin. These aneurysms may occur alone or with other cardiovascular anomalies. They are usually incidental findings at autopsy and seldom produce clinical manifestations. However, there are two reports of serious cardiac arrhythmias of many years duration that were attributed to the presence of septal aneurysms (Rogers *et al.*, 1952; and Clark and White, 1952).

The demonstration of a localized bulge of the left ventricular septum in a patient studied by angiocardiography is herein reported. Even though autopsy confirmation of a ventricular septal aneurysm is lacking, the distinctive features of the angiocardiogram strongly favour such a diagnosis. Further evidence for this conclusion is provided by comparison with a membranous ventricular septal aneurysm recently noted as an incidental finding at autopsy. The purpose of this report is to describe the angiocardiographic appearance of a suspected ventricular septal aneurysm and to propose criteria for the diagnosis of such aneurysms during life.

Case Report

A 60-year-old white housewife has been observed in the clinic and hospital for nearly five years. Cystitis was found on her first visit during 1950 and treated successfully. Subsequently she complained of mild dyspnœa and a routine chest roentgenogram revealed infiltration in the first right anterior interspace and an increase in the right hilar shadows. The heart appeared to be somewhat enlarged (Fig. 1A). Increased pulsation of the right descending pulmonary arterial branches was noted on fluoroscopic examination and an angiocardiogram was requested. Angiocardiography was normal except for a localized bulge to the right of the ventricular septum (Fig. 2).

During the five years under observation, the patient has had many complaints consisting of epigastric pain and discomfort. Studies, of the biliary, gastro-intestinal, and urinary systems revealed no abnormalities. The blood pressure was normal, 130/80. Standard, præcordial and vector electrocardiograms were normal except for left axis deviation and a P–R II of 0·21 sec. The heart examination was normal; no murmurs were elicited; the rhythm was normal sinus. Studies of the blood including the serologic test for syphilis were also normal. Tuberculin skin tests in all dilutions were negative. Biopsy of two skin papules failed to show sarcoidosis and no cervical, axillary, or inguinal masses have appeared. Roentgenograms of the chest during the five years have shown no change in appearance of the lungs, heart, or hilar structures.

Discussion

The embryological development of the membranous ventricular septum has been reviewed by Lev and Saphir (1936, 1938) and Rogers *et al.* (1952). The membranous ventricular septum is in part derived from endocardial cushion tissue and is intimately related to the closure of the atrioventricular canal. The closure is concerned with the union of tissues from the dorsal and ventral endocardial cushion systems, the primary interatrial septum, and the muscular interventricular

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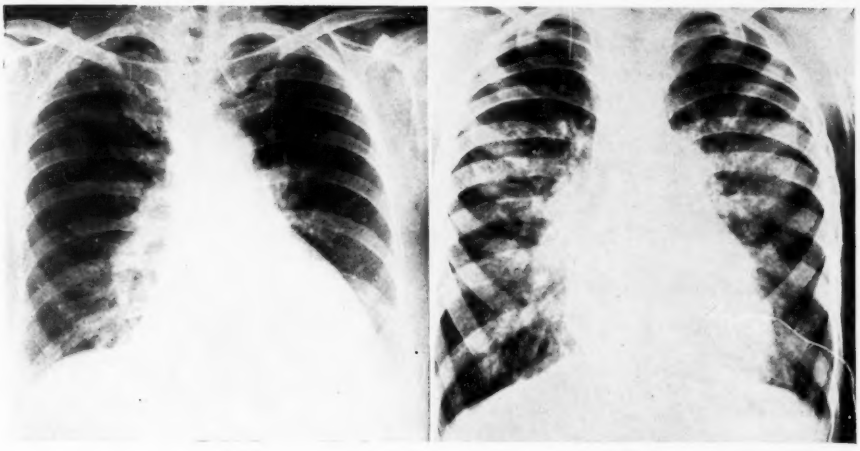

A B

FIG. 1.—(A) Teleradiogram from a woman, aged 60, showing slight increase in the size of the heart and prominence of the descending right pulmonary arterial branches. There is also minor right infraclavicular pulmonary infiltration. (B) Teleradiogram from an 8-year-old boy who died of bronchiectasis, bronchopneumonia, pulmonary emphysema, and cor pulmonale associated with fibrocystic disease of the pancreas. Note the enlarged heart, prominent pulmonary artery, and diffuse pulmonary fibrosis.

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Fig. 3 is an autopsy specimen, showing an aneurysm of the membranous portion of the ventricular septum—an incidental finding in an eight-year-old boy. Death was due to bronchiectasis, broncho-pneumonia, pulmonary emphysema, and chronic cor pulmonale that resulted from long-standing pulmonary disease associated with fibrocystic disease of the pancreas (Fig. 1B). The aneurysm consisted of a one-cm. pouch which bulged from the membranous part of the interventricular septum into the right ventricle and was attached to a tricuspid valve leaflet. The heart weighed 180 g. (expected weight 110 g.). The right atrium and ventricle were much dilated; the right ventricle was hypertrophied and measured 8 mm. The pulmonary artery was conspicuously dilated. The left atrium and ventricle were normal; the left ventricle wall measured 8 mm. No communication between the ventricles was noted and the fossa ovalis was closed. All the valves were thin, smooth, and intact, and had normal measurements; the coronary arteries contained no lesions.

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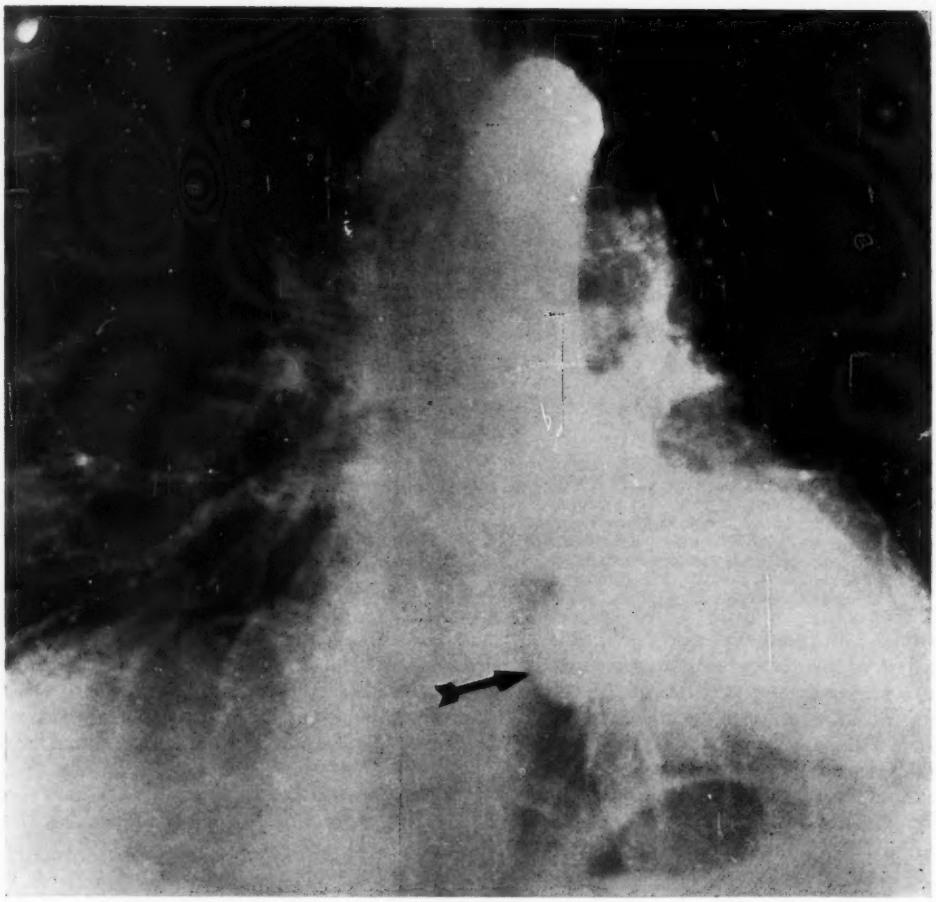

FIG. 2.—Frontal angiocardiogram (36-in. target film distance) shows normal opacification of the pulmonary veins, left ventricle, and aorta. Note the ventricular septal aneurysm (arrow).

therapy. During the two years under observation no cardiac murmurs were heard. The cardiogram showed right ventricular hypertrophy and right axis deviation.

In our living patient overt evidence of heart disease had not appeared during five years observation. Sarcoidosis was suspected at first because of the negative tuberculin tests and fullness of the right hilum which suggested mediastinal adenopathy, but skin biopsies failed to establish the presence of such a lesion and eye, lymph node, bone, kidney, or liver manifestations of sarcoidosis were never found. Bates and Walsh (1948) and Stephen (1954) reported sudden death of patients with sarcoidosis who had generalized sarcoidosis with myocardial and interventricular septal involvement at autopsy. The long survival period and absence of cardiac pain makes it unlikely that our patient has a septal aneurysmal due to sarcoid involvement of the heart.

As a rule, aneurysms of the membranous portion of the ventricular septum are of no great clinical importance. However, Rogers *et al.* (1952) point out that review of reported cases discloses that septal aneurysms may be sites of thrombus formation, superimposed bacterial endocarditis, and

perforation. They may also be factors in the development of subaortic stenosis (Rae, 1936) and aortic insufficienty (Leckert and Sternberg 1950).

Serious cardiac arrhythmias presumably due to ventricular septal aneurysms have been reported in two patients. Rogers *et al.* (1952) described a case with extreme cardiac irritability of ten years duration: during life, there were attacks of auricular fibrillation, A-V nodal rhythm, paroxysmal auricular tachycardia, sinus tachycardia, and idioventricular rhythm; clinical evidences of myo-

FIG. 3.—Incidental aneurysm of ventricular septum found in an 8-year-old boy. Aneurysm of the membranous portion of the left ventricular septum is located below the aortic cusps (arrow).

cardial infarction was present four years prior to death, and post mortem, in addition to a septal aneurysm, there was also a small ventricular septal infarction. Clark and White's (1952) patient had an aneurysm of the ventricular septum as the sole significant finding at autopsy: there was evidence of A-V block for 26 years prior to death, at first partial and later complete; death at the age of 47 was due to a series of Stokes-Adams attacks which were set off by paroxysmal ventricular flutter followed by ventricular tachycardia, ventricular standstill and complete A-V dissociation. Of interest, was the absence of bundle of His tissue in the carefully studied block sections of the entire aneurysm; histologically the aneurysm was composed of acellular collagenous tissue only.

The angiocardiographic demonstration of a localized bulge high in the left ventricular septum extending towards the right ventricular cavity is striking (Fig. 2). A filling defect of the right ventricle corresponding to the aneurysm was not recognized when the right ventricle was visualized. This may be because of the frontal positioning of the patient for angiocardiography. Had abnormality of the ventricular septum been anticipated, the left anterior oblique projection would have

been selected and would have provided a true lateral view of the ventricles and septum (Dotter and Steinberg, 1951). The characteristic appearance of the localized bulge of the left ventricular septum in a patient relatively free of disease of the heart is believed to be strong evidence for the presence of an isolated ventricular septal aneurysm. Such a lesion has long been known to occur without clinical manifestations and has often, as in this case, been an incidental finding.

Summary

A localized bulge high in the ventricular septum towards the right ventricle was recognized in the angiocardiogram of a woman, aged 60, who had a slightly prolonged P–R interval on electrocardiography and who was otherwise free of heart disease. On the basis of the angiocardiographic finding the diagnosis of an aneurysm of the membranous ventricular septum during life is proposed.

Although autopsy proof of the presence of the ventricular septal aneurysm is not available, the angiocardiographic diagnosis in this case seems warranted. The occasional occurrence of serious unexplained cardiac arrhythmias makes the diagnosis of ventricular septal aneurysm of more than academic interest.

Thanks are due to the Department of Pathology for permission to report the post-mortem findings in Case 2.

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PATENT DUCTUS ARTERIOSUS

A FOLLOW-UP STUDY OF 73 CASES

BY

J. A. COSH

From the University of Bristol and the Bristol Royal Infirmary

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The best known studies of the eventual effects of patency of the ductus arteriosus are based upon autopsy results. They suggest a high incidence of serious complications such as bacterial endocarditis and congestive heart failure. Table I summarizes the average age at death, and the incidence rates of bacterial endocarditis and congestive heart failure in three published series. Maude Abbott's (1937) survey of 92 cases included 20 who died under 5 years of age, and 16 who died of causes not directly attributable to the patent ductus. Keys and Shapiro (1943) calculated that, at 17 years of age, the normal expectation of life was halved if the ductus were patent. Commenting on these figures, Brown (1950) points out that " our ideas are mainly based on post-mortem cases and take little account of the living. . . . The adult case of patent ductus is a rare visitor to the clinic and the condition appears to be equally rare on post-mortem examination. . . . There must be spontaneous closure of the ductus more often than is generally realized, or cases are missed when failure supervenes and the characteristic physical signs disappear."

TABLE I

PATENT DUCTUS ARTERIOSUS—NECROPSY FINDINGS

Authors	No. of cases	Average age at death (in years)	Deaths from subacute bacterial endocarditis	Deaths from heart failure
Maude Abbott, 1937	92	24	27 (29%)	24 (26%)
Bullock *et al.*, 1939 (excluding children under 4 years)	80	29	42 (53%)	18 (23%)
Keys and Shapiro, 1943 (excluding children under 17 years)	60	36	25 (42%)	17 (28%)

For contrast with studies based upon autopsy results there are a few reports on the progress of living patients with patent ductus arteriosus. Wilson and Lubschez (1942) followed 38 children; one died suddenly from an unknown cause, but the remainder did well and were free from complications; few, however, were followed into adult life. Welti and Koerperich (1948) traced 41 out of 54 patients; 7 had died, and the age of the 34 survivors ranged up to 53 years; 14 were women who had borne children, three having had three children each; all the survivors were able to lead reasonably active lives, but in general had some limitation of physical effort; and 24 had dyspnœa and 21 cardiac enlargement. Benn (1947) reported on the progress of 46 patients, mostly children, contrasting the freedom from disability in 30 who had been diagnosed on routine school medical examination with 16 referred to hospital from other sources, 5 of whom developed bacterial endocarditis.

Campbell (1955), reviewing 160 cases of patent ductus, found the majority of younger patients well and symptom-free, but those in the fourth decade or older tending to develop dyspnœa, cardiac enlargement, or failure. Deterioration in middle or later life was also mentioned by Gross (1952) in his report on 525 cases coming to surgery. To some extent these series must consist of selected cases, many being referred for an opinion with surgery in view.

Surveys based upon living patients suggest, therefore, that the prognosis with patency of the ductus is not as bad as autopsy studies indicate.

The Present Study

An account follows of the 73 patients with simple patency of the ductus arteriosus referred to the clinics or wards of the medical unit at Bristol in the past 30 years, under the care of the late Dr. Carey F. Coombs or Professor C. Bruce Perry. In all the diagnosis was made clinically on the presence of the characteristic murmur, and in none did it appear that any other lesion was present. The correctness of the clinical diagnosis was borne out by the finding of a patent ductus in the 28 coming to operation, and in the 5 coming to autopsy; one of the latter, however, was found to have a ventricular septal defect also. Included in this series are Benn's 46 cases, and the complications reported by him appear also in the inclusive survey made here. All surviving patients have been examined by the author except four who could not be traced, five who live at a distance but on whom current medical reports are available, and one who is known to be well but refuses to attend for examination.

The *present state* of the 73 may be summarized as follows: surviving with ductus not ligated, 34; surviving with ductus ligated, 28; died, 7; and follow-up incomplete, 4 cases.

Sex Incidence. Fifty-three were female and 20 male, giving a female preponderance of 2·7 to 1, similar to that usually found.

Progress of Patients

In Relation to Source of Patients. The 73 patients have been divided into 4 groups according to the manner in which they were referred to hospital. Group I consists of 33 patients originally sent up to the children's heart clinic after discovery of a murmur on routine school medical examination. Their age when first seen averaged 7 years, and 21 years when last seen or when the ductus was ligated. Only 3 of the 33 had symptoms, two having dyspnœa and one a chest infection. Twenty-one remain well without surgery, and of these four have lost their continuous murmurs; seven had the ductus ligated, of whom two had recently been cured of bacterial endocarditis; one other developed bacterial endocarditis and died; one boy died of diphtheria; and three were lost to follow-up.

In Group II are 20 patients referred to a general out-patient clinic from practitioners in or near the city; their age on first attendance averaged 13 years, and 21 when last seen or when the ductus was ligated. Fifteen, including three who were pregnant, had no symptoms; of the five with symptoms, two had dyspnœa, two had chest infections, and one palpitations from sinus tachycardia. Ten remain well without surgery, eight had the ductus ligated, one died of pulmonary embolism, and one was lost to follow-up.

In Group III are 8 patients who first came to hospital as direct admissions. Their ages averaged 14 years initially, and 23 when last seen or when the ductus was ligated. Three came with bacterial endocarditis, of which they died; three were children with respiratory infections. One was admitted for investigation with tachycardia: some years later her condition deteriorated, and she finally died in congestive failure. The eighth came in for investigation of vomiting; she is now well, although she has some dyspnœa, 35 years later. Of the 8, four died of causes attributable to the ductus, three survive without surgery, and one has had the ductus ligated.

Group IV consists of 12 cases admitted to the medical wards from other hospitals specifically for surgery. Seven were symptom-free; one was a girl of 4 years with recurrent chest infections and

cardiac enlargement; the remaining four had dyspnœa, the most severe being a miner of 24 years who had recently developed congestive failure with auricular fibrillation. In all 12, the ductus was ligated.

As pointed out by Benn, Goup I is probably a truly representative group of unselected patients with patent ductus of 5 or more years of age, being composed of cases found on routine medical examination of the great majority of Bristol school children. On the other hand, Groups II and III together represent cases normally referred to hospitals and clinics. Of the 33 in Group I, 30 (91%) were initially symptom-free, in 7 (21%) the ductus was ligated, and 21 (63%) survive without ligation. Of the 28 in Groups II and III, 15 (54%) were initially symptom-free, in 9 (32%) the ductus was ligated, and 13 (46%) survive without ligation. In each class three patients developed bacterial endocarditis. The two classes differ in that the initial average age in Group I was 7 years, and in Groups II+III 14 years; but Group I was followed for 14 years on the average, with the ductus patent, and Groups II+III for 8 years only.

It appears, then, that in a representative and unselected group of 33 patients with patent ductus, the incidence of symptoms was lower, and the subsequent course rather more favourable, than among 28 patients referred to hospital in the usual way. The incidence of bacterial endocarditis was similar in the two classes.

Deaths. Seven among the 69 traced patients have died. The causes of death were bacterial endocarditis in four, pulmonary embolism in one, congestive heart failure in one, and diphtheria in one. The patient dying from pulmonary embolism was aged 39 years, and is the subject of a separate report (Cosh, 1956). The patient with congestive failure died at home, aged 33, and no autopsy was performed; at the age of 16 she was known to have cardiac enlargement, a systolic thrill, and the cardiogram of left ventricular hypertrophy.

Bacterial Endocarditis. Six patients in the series developed bacterial endocarditis. Four died before penicillin was introduced, and the two who survived were both infected with *Streptococcus viridans* and recovered after the usual treatment; in each the ductus was ligated a few weeks later. The ages at which bacterial endocarditis arose were 11, 21, 25, and 36 years in those who died, and 9 and 23 years in those who recovered, giving an average of 21 years. This compares with average ages of 24 years in Bullock's series and 27 years in Keys and Shapiro's series.

The incidence of 6 cases among 69, or 9 per cent, is far lower than the rates quoted in Table I. The difference must be attributed to the facts that in studies based upon published autopsied cases, the incidence of infection is exaggerated; that survivors with patent ductus in this series continue to run the risk of infection; and that present-day risks are lessened by the prophylactic use of penicillin.

In all, the 73 patients reviewed here lived a total of 1451 years up to the time of their last examination or to ligation of the ductus. As 6 patients became infected, this represents an infection rate of 0·4 per cent per annum. At this rate, among the 34 patients surviving without surgery, one case of infection might be expected in every 7 years.

Progress of Patients without Operation. Ten male and 24 female patients have not been submitted to operation. Their average age is 26 years, and their ages are distributed as follows:

5 to 9 years	1
10 to 19 ,, ...	10
20 to 29 ,, ...	10
30 to 39 ,, ...	10
45 to 56 ,, ...	3

The great majority lead normal lives. Seven are aware of some dyspnœa or fatigue on exertion, but are not appreciably handicapped by this. Of the 10 males, two are normally active schoolboys, and eight are men in various occupations, two having served in the army. Of the 24 females, five are schoolgirls, nine are unmarried women working or studying, and ten are married, eight of these having borne children.

Pregnancy. Between them the 8 mothers have borne 23 children. One has had ten children, two have had three children each, two have had two each, and three have had one each. Some women were aware of fatigue or dyspnœa towards the end of pregnancy, but in one only was admission to hospital advised before term. Delivery occurred normally in all.

Among the seven patients who died, two had borne children. One woman, who died at the age of 27 years from bacterial endocarditis, had had two normal deliveries. The other, who died aged 39 from pulmonary embolism, had had one child without difficulty, but her second pregnancy was terminated by hysterotomy at the fourth month, as she suffered from dyspnœa and fatigue and had considerable cardiac enlargement.

On clinical grounds it is unlikely that the ductus is a wide one in any of the eight surviving women who have borne children. Nor have they signs suggesting pulmonary hypertension. Three have slight cardiac enlargement, with cardio-thoracic ratios of 50–55 per cent, and one other has left ventricular hypertrophy on the electrocardiogram. Other reports of successful pregnancy in the presence of a patent ductus are given by Bramwell and Longson (1938), Mendelson and Pardee (1941), Gilchrist (1945), and Kernohan (1953). In general it is clear that pregnancy is well tolerated in the presence of a patent ductus of small or moderate size.

Changes Noted in the Murmur and Thrill. In 60 of the 73 cases, the murmur was on all occasions typical in character and situation, agreeing with the description of Gibson (1906). Seven children, when first seen, had a systolic murmur only in the pulmonary area, and a continuous murmur was noted later. The ages at which the continuous murmur was first heard were: 3, 3, 4, 4, 5, 5, and 6 years. In five of these seven the initial systolic murmur was accompanied by a thrill, which could still be felt, in systole only, after the murmur had become continuous. These 5 children were later chosen for operation on the grounds of poor growth, dyspnœa, or cardiac enlargement.

In four patients the continuous murmur has disappeared; two of these have already been mentioned by Benn (1947). All four are symptom-free, with no enlargement of the heart on X-ray, normal blood pressures, and normal electrocardiograms. Further details are as follows.

J. C. A girl was examined annually between 8 and 12 years of age; on each occasion a continuous murmur was heard; there was no thrill. When 15 she had pulmonary tubercle with positive sputum. Examination at ages 15, 21, 25, 31, and 34 revealed a faint systolic murmur only.

G. I. A boy, said to have congenital heart disease at one year of age, was found to have a continuous murmur at 10 years of age. At 23 he was serving as an able seaman with the Royal Navy: a soft basal systolic murmur only was heard. At ages 27 and 33, he was well and had no murmurs.

B. G. A girl was seen periodically between 5 and 16 years of age, a continuous murmur being heard each time. When she was 5, there was a systolic thrill at the pulmonary area, but not thereafter. When 23, she was well and working, and there were no murmurs.

L. S. A boy had a pulmonary systolic murmur when 4, and a continuous murmur at 5 and 8 years old. When 29, he was seen by Dr. J. W. Brown, who found no abnormal physical signs.

Disappearance of the continuous murmur has been described when congestive failure develops (Campbell and Hudson, 1952), and the murmur is absent with severe pulmonary hypertension (Cosh, 1953; Dammann *et al.*, 1953; Yu *et al.*, 1954; Lukas *et al.*, 1954; and Whitaker *et al.*, 1955), Neither of these conditions apply to the four cases described here, particularly as signs of pulmonary hypertension and right ventricular hypertrophy were absent. It seems more likely that the loss of the murmur may be explained by shrinkage of the ductus or its actual closure. Apparent delayed closure of the ductus has been noted by Brown (1950) in five cases, by Shapiro and Keys (1943) in two, and by Gilchrist (1945) in one.

A *thrill* at the pulmonary area was felt throughout the follow-up period in 35 patients, and was consistently absent in 24. It is of some interest to compare the later course of these two groups. Of the 35 with a thrill, 22 were chosen for operation on account of symptoms, poor growth, or cardiac enlargement; 5 others died. Of the 24 with no thrill, only 5 came to surgery, and these were symptom-free without cardiac enlargement ; two died, of bacterial endocarditis. These figures suggest that the presence of a thrill is a useful guide to the prognosis, presumably because it signifies the presence of a wide ductus.

Radiology

Radiographs of 65 patients were available, in the majority covering periods of several years, and estimates of heart size were made from the cardiothoracic ratio. Thirty-one patients had ratios under 50 per cent; in 21 there was slight enlargement (ratio 50–54%), in 8 moderate enlargement (ratio 55–59%) and in 5 much enlargement (ratio over 60%). No patient during the follow-up period had an increasing heart size according to this grading, although it decreased in some. Apart from the reduction in cardio-thoracic ratio seen in the first five years of life, a reduction was noted to have occurred spontaneously in 4, and to have followed ligation of the ductus in 9 patients.

The size of the main pulmonary artery was estimated by measurement of the " pulmonary artery index " (Evans, 1943). This is the distance from the junction of the superior vena cava and the right atrium on the right heart border, to the most prominent point on the outline of the pulmonary artery on the left heart border. It normally measures less than 7 cm in the adult. In 41 out of 65 patients this index was under 7 cm; in 17 it was 7–8 cm, and in 7 over 8 cm. An increasing index was naturally found in children up to adolescence, but only one adult had a progressive increase in size of the pulmonary artery (Cosh, 1956). No patient had a measureable decrease in the size of the pulmonary artery after ligation of the ductus. Only in two patients with gross dilatation of the pulmonary artery (index over 9 cm) was there any obvious correlation between the size of the pulmonary artery and the severity of the patient's symptoms, the size of the heart, or the degree of vascularity of the lung fields.

Fluoroscopy was carried out on 45 patients. In 5 there was no visible pulsation in the pulmonary arteries; in 21 the pulsation was minor and only in the main branches; in 15 it was moderate or brisk; and in 4 it was striking, with a hilar dance. Some correlation was found between the degree of pulsation seen and the systemic pulse pressure; in 11 of the 19 (58%) with moderate or striking pulsation of the main pulmonary arteries the systemic pulse pressure was over 50 mm/Hg. In only 6 of the remaining 26 patients (23%) was the systemic pulse pressure as large as this.

Cardiac enlargement was not found more frequently among the older patients, for, of the 13 aged 30 years or more, 8 had cardiothoracic ratios below 50 per cent. In 9 of this group there was dilatation of the aortic arch and increased prominence of the aortic knuckle; 4 of these had calcification in the aortic wall or in the region of the ductus, best revealed by tomography in the lateral position.

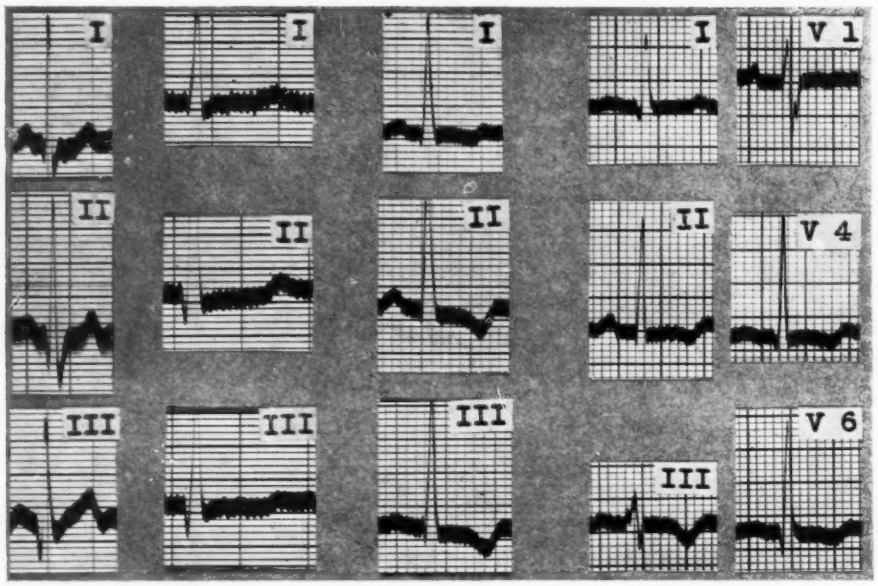
The Electrocardiogram

Electrocardiograms were available in 69 cases, 54 having præcordial leads and 15 limb leads only. The majority were normal.

Left axis deviation (less than $-20°$) was found in 6; in 4 of these præcordial leads were available, but only one showed left ventricular hypertrophy. *Right axis deviation* (over $+100°$) occurred in 2; one was an asthmatic girl with a vertical heart, and the other a woman with pulmonary hypertension and right bundle-branch block.

Left ventricular hypertrophy with strain pattern (S–T depression and/or T inversion in leads I, aVL, or V 4, 5, or 6) was seen in 7 patients. Each had a systolic thrill. Four were seen in childhood, and were then underweight. The three adults were dyspnœic, and one died in congestive heart failure. The 6 survivors with left ventricular hypertrophy had enlarged hearts: in 5 the ductus has been ligated and they are well, and in the sixth it is still patent; she is 26 and has borne one child, and has no symptoms. She is the only patient in whom past records show the development of left ventricular hypertrophy; the first changes were seen at the age of 9 (see Fig. 1 and 3, E.W.).

Auricular fibrillation was seen twice. One man with pulmonary hypertension and a greatly enlarged heart spontaneously developed auricular fibrillation and congestive failure when he was 24: five months later the ductus was ligated, but fibrillation has persisted, without reduction in the size of the heart, and after two years he again developed heart failure, from which he has recovered. Co-existent rheumatic heart disease cannot be excluded. A similar patient, who continued to



Age: 2 years. 7 years. 9 years. 23 years.

FIG. 1.—The development of electrocardiographic changes of left ventricular hypertrophy. *Age 2*, normal record. *Age 7*, T waves diminished in amplitude. *Age 9*, T waves biphasic in I, inverted in II and III. *Age 23*, the axis has changed from vertical towards horizontal; T remains inverted in II and III; V4 and V6 show tall R and biphasic T waves.

show fibrillation and died suddenly four years after legation of the ductus, is described by Dry *et al.* (1948); autopsy showed no signs of rheumatic heart disease. The second case of auricular fibrillation was a man of 35 with pulmonary hypertension and a large heart, in whom arrhythmia followed ligation of the ductus; sinus rhythm returned two weeks later after quinidine.

Effect of Operation on the Electrocardiogram. Cardiograms were obtained before and after operation in 20 cases. There was no significant change in 14 of these, but the only two patients with S–T depressions in lead I before operation both had normal records afterwards. Other changes noted were of a minor nature. Landtman (1954), reviewing cardiographic changes resulting from ligation of the ductus, reported that 18 of 25 patients with S–T depression in lead I associated with left ventircular hypertrophy lost this depression.

Effect of Age on the Electrocardiogram. Of the 13 patients aged over 30 years, 11 had completely normal 12-lead tracings, one had left ventricular hypertrophy, and one had right bundle-branch block. It appears that age alone has no particular influence on the electrocardiogram in the presence of a patent ductus.

Children's Weights. Sutcliffe and Canham (1950) have established the normal range of weights of English school children aged 5–17 years. From their figures for the percentile distribution of weights 6 groups may be defined, which for convenience may be named A to F (Fig. 3). A quarter of all normal children are in the upper two groups, A and B; half are in the middle groups, C and D; and a quarter are in the lowest groups, E and F.

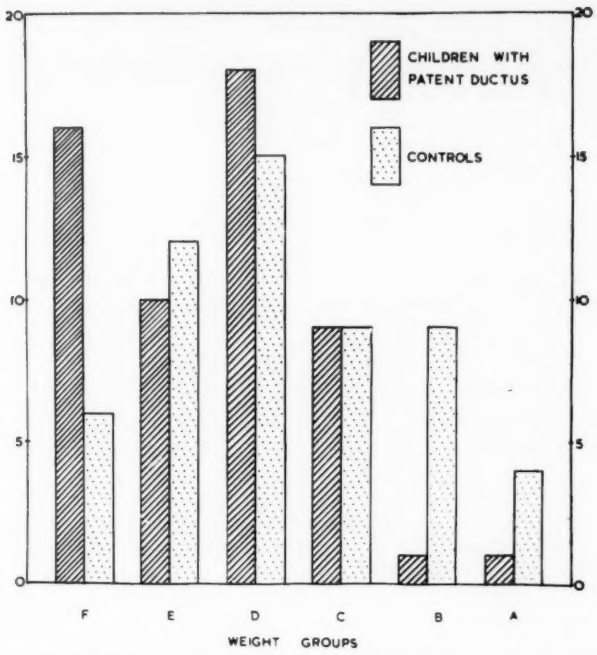


FIG. 2.—Distribution of weights of 55 children with patent ductus and of 55 individually-matched normal controls. They are shown in 6 weight groups, derived from the data of Sutcliffe and Canham (1950); A is the heaviest group and F the lightest. Children with patent ductus tend to occupy the lower weight groups.

The weights of 55 children with patent ductus, with an average age of 8 years, were classified in these six groups. For comparison, a classification was also made of 55 normal Bristol school children, matched individually with the 55 patients by age and sex. Fig. 2 shows not only that children with patent ductus fall more often into the lower groups than the upper, but also that their distribution in these groups is different from that of the controls. This difference is statistically significant, and would arise by chance less often than once in a hundred times.

Many of the children with patent ductus were followed through their school years: 21 out of 30 remained in the same weight group as they grew older; 5 improved by one or two groups; and 4, though gaining in weight, declined by one or two groups.

The Effect of Operation on Weight. The effect of ligation of the ductus upon the weight curve was studied in 13 children, who were followed after operation for periods ranging from 1 to 5 years. All gained weight, but 9 remained in the same group as before operation, while 4 improved by one or two groups. Fig. 3 illustrates the progress of four girls, two of whom had the ductus ligated, and two not.

The gain in weight that followed ligation of the ductus was thus, in the majority, no more than might have been expected without ligation. Indeed, improvement in weight relative to the normal standards for a child's age and sex may even lag behind improvement as judged by other criteria; two girls were observed to remain in a low weight group after surgery, although their hearts diminished in size and S–T depressions in lead I were corrected.

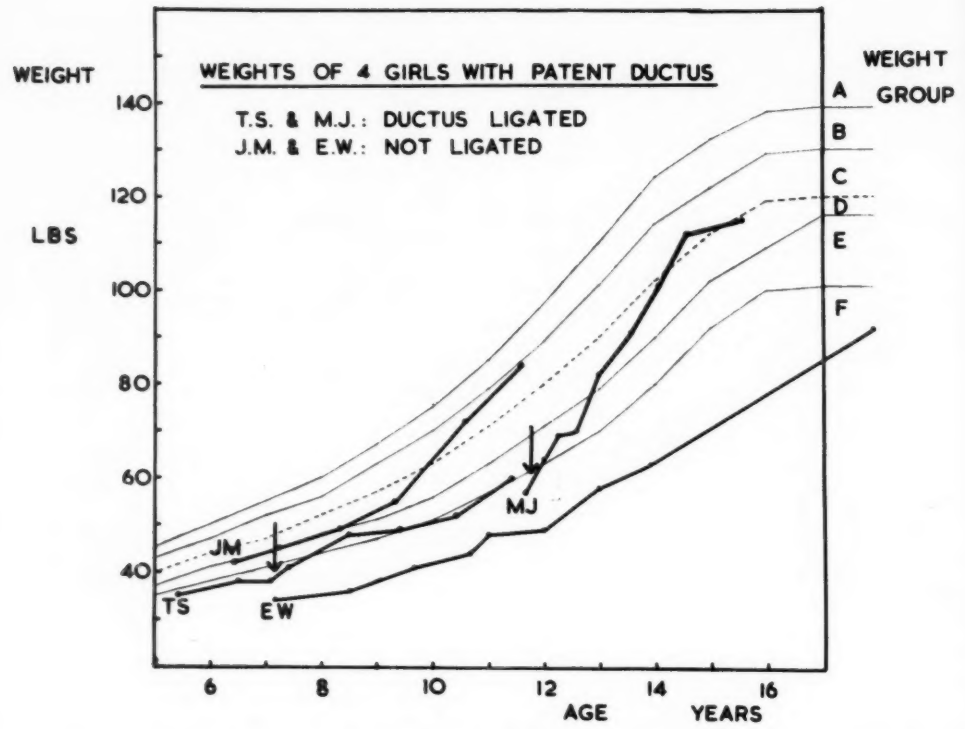


FIG. 3.—Examples of weight curves in 4 girls with patent ductus. The 5 background lines separate 6 weight groups, A to F, and the dotted line between groups C and D shows the median weight for girls. E. W. (see also Fig. 1) remained obviously under-weight, in group F throughout, but J. M.'s weight improved spontaneously as she grew older. The weight of T. S. remained low for her age, in spite of ligation, indicated by the arrow. M. J.'s weight improved dramatically after ligation.

Selection for Surgery. As already indicated, patients were selected for operation when it was clear that they had symptoms of dyspnœa or fatigue due to the presence of the patent ductus, or if they were significantly under-weight, or had enlarged hearts, or had had bacterial endocarditis. Exceptions were those in Group IV, who were referred from other centres specifically for surgery; all of these had the ductus ligated irrespective of symptoms. Operations were performed by Professor R. Milnes Walker or Mr. R. Belsey. There were no deaths and few post-operative complications (Cade, 1954). Recanalization has occurred in one.

DISCUSSION

While this review shows an appreciable mortality and infection rate among patients with patent ductus, it suggests a much better prognosis than do those reports that are entirely based upon autopsy findings. It shows, too, a lower morbidity rate in unselected cases than among those usually referred to hospital. Other features are the general well-being of the adult patients, the occurrence of pregnancies and childbirth without complication, and the occasional apparent closure of the ductus in early adult life.

Those patients who survive without operation are a selected group in that the worst cases have either died, or have had the ductus ligated, implying that the ductus is not widely patent in those who have not had surgical treatment. The first 21 cases in the series, however, all diagnosed before 1934, are unselected in that none have had the ductus ligated. Of these 21, four have died, two of bacterial endocarditis, one of heart failure, and one of diphtheria; two cannot be traced; but the remaining 15 are well, and include the 4 who have lost their continuous murmurs.

Surgery is certainly indicated when the signs suggest that the ductus is a wide one, and wise when the ductus has recently been infected. If the ductus is small and causing no disability in an otherwise healthy child, surgery is justified, for the risks of ligation are now less than the small risks of leaving the ductus patent. But this survey suggests that in an adult with few or no symptoms, and little or no cardiac enlargement, the ductus may safely be left open as long as care is taken in preventing bacterial endocarditis. In such a patient there is no contra-indication to childbirth.

Summary

Of 73 patients with patent ductus arteriosus known to one clinic over the past thirty years, 69 have been traced. Seven have died, of causes that are directly attributable to the ductus in five and indirectly in one. Six developed bacterial endocarditis, representing an incidence rate of 0·4 per cent per annum.

The ductus was ligated in 28, the usual indications being dyspnœa, fatigue, poor physique in childhood, cardiac enlargement, or recent bacterial endocarditis.

The ductus was not ligated in 34, whose average age is now 26 years. None suffer serious restriction of activity, though 7 are aware of dyspnœa, and 8 have some cardiac enlargement. In 4 the continuous murmur has disappeared.

Twenty-one of the 35 patients with a thrill, and only 5 of the 24 without a thrill, were selected for operation.

Childbirth occurred 23 times in patients with the ductus patent, without difficulty or complication. Only one patient required termination of pregnancy with sterilization.

Children with patent ductus were significantly under-weight when compared with normal controls. Only 4 out of 13 showed a significant improvement in weight in the years following ligation of the ductus.

I wish to thank Professor C. Bruce Perry, who was in charge of these patients and suggested this survey, for his help and criticism. My thanks are also due to Dr. J. W. Brown for his report on one of the patients, to Dr. Gustav Herdan, Lecturer in Statistics, University of Bristol, for his analysis of the weight figures, and to Dr. A. L. Smallwood, Senior School Medical Officer, Bristol, for the weights of normal control children.

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EFFECTS OF INTRAVENOUS DIGOXIN IN UNCONTROLLED AURICULAR FIBRILLATION

BY

JOHN HAMMOND AND WILLIAM WHITAKER

From the University Department of Medicine, The Royal Hospital, and the Regional Cardiovascular Unit, The City General Hospital, Sheffield

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Since William Withering in 1785 first recognized the effect of digitalis in the relief of dropsy and in slowing the heart rate, the drug has been used extensively in the treatment of congestive heart failure and its mode of action has been the subject of many studies. MacKenzie (1910) and Lewis (1919) taught that digitalis was of greatest value in cases of congestive heart failure with auricular fibrillation and considered that its therapeutic effect was due to slowing of the heart rate. MacKenzie (1918) did, however, admit that it should be used in cases of congestive heart failure with sinus rhythm. Wenckebach (1910) considered that the drug was of value in all types of heart failure.

Broadbent (1917), from clinical experience, and Sutherland (1919) thought digitalis to be of use in cases of heart failure with regular rhythm, especially when this was rapid. Christian (1919, 1922) and West and Pratt (1920) found a satisfactory response in cases with sinus rhythm and Luten (1924) and Marvin (1926), studying the effect of digitalis in patients with congestive heart failure and regular rhythm, concluded that the response depended largely on the underlying ætiology, and was better in patients with myocardial insufficiency than in cases with syphilitic and rheumatic heart disease. Gavey and Parkinson (1939) noted that digitalis frequently caused diuresis in patients in congestive heart failure with sinus rhythm, although the response was usually not so dramatic as with auricular fibrillation, and concluded that digitalis was indicated in congestive heart failure whatever rhythm was present.

The action of digitalis on the heart and circulation has been extensively studied in animals and human beings. Eppinger *et al.* (1924) showed that the cardiac output decreased in a patient with heart failure after treatment with digitalis, although there was clinical improvement. Harrison and Leonard (1926), using the direct Fick principle, found that the cardiac output fell in normal dogs after the intramuscular injection of digifolin, and Burwell *et al.* (1927) found the same effect in men after oral digitalis. Kininmonth (1928) found that digitalis produced variable changes in cardiac output in patients with heart disease and concluded that an increase was most likely to occur where the output was initially low. Ringer and Altshule (1929) also found that the cardiac output increased after giving digitalis to patients with congestive heart failure and auricular fibrillation, but only rarely if sinus rhythm was present. Dock and Tainter (1930) thought that the fall in cardiac output and venous pressure that occurred in normal dogs following an intravenous injection of digitalis was caused primarily by constriction of the hepatic veins so that blood was dammed back in the liver and portal system. The importance of this mechanism was refuted by Wood (1940), who showed that the liver decreased in size in patients with congestive heart failure following digitalis therapy. Stewart and Cohn (1932) and Stewart *et al.* (1938) found that the cardiac output was lower than normal in patients with congestive heart failure and that digitalis increased it in these patients and lowered it in normals. They noted that digitalis caused the size of the heart to decrease in both normal and abnormal patients and concluded that its action was to decrease the size of the heart and increase the extent of ventricular contraction. They found that the venous pressure fell if it was previously elevated. The effects were the same in patients with sinus rhythm as in those with auricular fibrillation.

Following the introduction of cardiac catheterization, numerous workers adopted this technique, since it provided a simple method of estimating cardiac output and recording directly blood pressures on the right

side of the heart. Studying the effects of intravenous digoxin in patients with congestive heart failure, McMichael and Sharpey-Schafer (1944) suggested that the drug acted primarily by altering venomotor tone and that the increase in cardiac output was largely due to the fall in venous pressure. However, subsequent studies by Bayliss *et al.* (1950), by Wood and Paulett (1949), and by Harvey *et al.* (1949) failed to confirm this and showed that digoxin had a direct effect on the failing myocardium.

Goodman and Gilman (1941) thought that the disappearance of œdema following digitalis therapy could be attributed to a fall in venous pressure and to improvement in renal function caused by an increase in cardiac output and the fall in renal venous pressure. More recently several observers have studied the changes in renal circulation following digitalis therapy and have attempted to relate the improved capacity to excrete salt and water to these changes. Eichna and Taube (1944) found that the diuresis following the intravenous injection of digoxin in patients with congestive heart failure was preceded by a fall in systemic venous pressure, though at times the latter fell and no diuresis ensued. Farber *et al.* (1951) and Davison and Gaddie (1951) also studied the effect of intravenous digoxin in patients with congestive heart failure and found that the renal plasma flow rose considerably in some cases indicating an increase in renal blood flow. The latter authors thought that this increase, which caused renal function to improve, was secondary to a rise in cardiac output. In a later study of the effect of intravenous digoxin on the systemic and renal circulation of patients suffering from congestive heart failure with uncontrolled auricular fibrillation, Eichna *et al.* (1951) found that the changes in renal plasma flow and glomerular filtration rate were much less consistent, smaller in absolute values, and slower in onset than changes in the cardiac output, heart rate, and venous pressure. They noted that a marked diuresis and increased excretion of sodium and chloride followed the injection of digoxin and thought that, in most patients, these were far greater than could be accounted for by changes in renal circulation and that digoxin might have a direct action on the renal tubules. This suggestion was supported by a moderate effect of digoxin in increasing sodium excretion in patients with non-cardiac œdema and in non-œdematous subjects observed by Farber *et al.* (1951).

Since Eichna *et al.* (1951) and Davison and Gaddie (1951) arrived at different conclusions about the effect of intravenous digoxin on renal function in patients who were in congestive heart failure, further investigation of this effect of digitalis appeared desirable. The present study was designed to investigate the effect of intravenous digoxin on renal function in patients with uncontrolled auricular fibrillation. Two groups were studied: in one the patients had clinical evidence of congestive heart failure and in the other they had never experienced this complication.

Material and Methods

Thirteen patients, of whom nine were women, and all suffered from uncontrolled auricular fibrillation were studied. Ten had chronic rheumatic heart disease; in six the lesion was mitral stenosis; in two mitral stenosis and incompetence, and in two mitral incompetence. Two cases had thyrotoxicosis and no cause was found for the auricular fibrillation in one. One man with mitral stenosis had also extensive osteitis deformans, and one woman with mitral stenosis subsequently died from polyarteritis nodosa. Six patients, had congestive heart failure, judged from the presence of peripheral œdema and rise of jugular venous pressure above the sternal angle in all phases of respiration, while the other patients had never experienced this complication. Nine patients had never been treated with digitalis previously; two had been off treatment for five and ten weeks respectively and two had received none of the drug for four and ten days respectively prior to investigation.

All observations were made about two hours after a meal with the subjects propped up comfortably in bed at an angle of approximately forty-five degrees. Cardiac output was calculated by the Fick principle from oxygen consumption, measured by collecting expired air in a Douglas bag, and from the differences in oxygen content of arterial blood, withdrawn from an indwelling needle in the brachial artery and mixed venous blood, withdrawn from the right atrium through a cardiac catheter previously introduced under fluoroscopic control. The hæmoglobin content of each blood sample was measured by a photoelectric colorimeter and from this the oxygen capacity was determined; the percentage oxygen-saturation was measured by a direct spectro-photometric method, and from these results, the oxygen-content of the sample was estimated. The renal plasma flow was measured by sodium-para-amino-hippuric acid clearance and glomerular filtration rate by inulin clearance, using the technical method described by Dick and Davies (1949). A priming injection of sodium-para-amino-hippuric acid and inulin was given and at the same time the patient drank 500 ml. of water. Thereafter plasma levels were maintained by a constant intravenous infusion of sodium para-amino-hippuric acid and inulin in a 5 per cent dextrose solution. The sustaining

infusion was given at the rate of 1·5 ml. per minute. The filtration fraction, the fraction of the plasma passing through the kidney that is filtered by the glomeruli, was calculated by dividing the glomerular filtration rate by the renal plasma flow. The renal blood flow was calculated from the renal plasma flow and the hæmatocrit. The renal fraction of the cardiac output was used to express renal blood flow as a percentage of total cardiac output. The systolic and diastolic blood pressures were recorded sphygmomanometrically and the value of the arterial mean blood pressure was assumed to be equal to the diastolic blood pressure plus one-third of the pulse pressure. The systemic vascular resistance, in dynes sec. cm.$^{-5}$ was calculated by dividing the product of the arterial mean blood pressure, in cm. Hg, the density of mercury, and the acceleration due to gravity, by the cardiac output in ml. per second. The renal vascular resistance was similarly estimated taking the perfusing pressure as the arterial mean blood pressure minus the renal venous pressure, which was assumed to be equal to the right atrial pressure measured by cardiac catheterization. The sodium in the urine was estimated by a flame photometer and the chloride by a silver nitrate potentiometric titration.

Observations were made during five accurately timed periods of urine collection of approximately twenty minutes each. The first two served as control periods and 1–1·5 mg. of digoxin was then given through the cardiac catheter over five minutes at the start of the third period of observation. Two further periods after this completed the procedure. Mixed venous and arterial blood samples were obtained as previously described at the mid points of each collection period and expired air was collected in a Douglas bag over two four-minute periods during the second and last periods of observation. The values given in the Table are the averages (*a*) for the observations and estimations made in the first two control periods, and (*b*) for those made in the last period of observation when the full effects of the digoxin had become apparent. The arterial mean blood pressures were calculated from the average of at least six readings of systolic and diastolic blood pressures taken during each period of observation.

Results

The results of the present investigations are summarized in the table and illustrated in Fig. 1 and 2. The six patients with congestive heart failure are grouped together in Section A, and the others without congestive heart failure are grouped in Section B.

Changes in the systemic circulation following digoxin. There was a reduction in heart rate within five minutes in all cases; the rate decreased rapidly during the first thirty minutes and then continued to fall more slowly (Fig. 1 and 2).

The systemic blood pressure rose in eight patients, five with heart failure and three without this complication. The systolic pressure increased more than the diastolic pressure, which usually showed little change. In the remaining five patients there was a reduction in systemic blood pressure, systolic and diastolic pressures falling within ten minutes in four, and after thirty minutes in one. The arterial mean blood pressure, calculated from the average systolic and diastolic pressures recorded before and after digoxin, showed an increase in six patients, a decrease in six, and no change in one, Case 5.

In five patients with heart failure, and in five without, there was a fall in right atrial pressure. This was greater in patients with heart failure, but in one without œdema but with an abnormally high initial venous pressure, there was a marked fall in right atrial pressure. In two patients without heart failure and in one with heart failure, who had received digitalis until four days prior to investigation, intravenous digoxin caused no fall in right atrial pressure.

The most dramatic changes in cardiac output occurred in four patients with congestive heart failure where the percentage increase in output was respectively 115, 30, 16, and 69. There was a slight increase in cardiac output in three patients without heart failure, but in all these the change was less than 14 per cent. In one patient with heart failure and in three without, digoxin caused no alteration in cardiac output. Two patients, one with and one without heart failure, showed a fall in cardiac output of 12 and 19 per cent respectively. Digoxin had no effect on the oxygen consumption and the changes in cardiac output were apparent from an alteration in the oxygen saturation of mixed venous blood.

From the changes in cardiac output and arterial mean blood pressure after the digoxin it was apparent that there had been a decrease in systemic vascular resistance in five patients with congestive

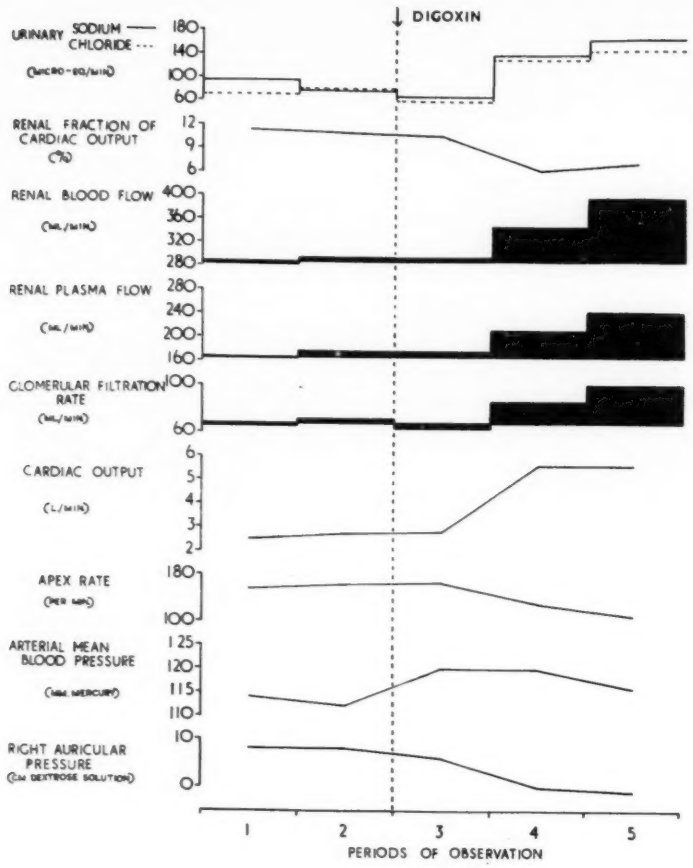

FIG. 1.—The effect of 1·0 mg. of intravenous digoxin on the systemic and renal circulations and salt excretion in Case 1.

heart failure and in three without this. In one patient with heart failure and in two without it, the systemic vascular resistance increased, and in two patients without heart failure it remained unchanged (Table).

Changes in the renal circulation following digoxin. An increase in renal blood flow, renal plasma flow, and glomerular filtration rate occurred in three patients with congestive heart failure, and an increase in renal blood flow and renal plasma flow unaccompanied by a change in glomerular filtration rate in two patients without heart failure. In the other three patients with heart failure and in the remaining patients without this, there was little or no change in renal blood flow, renal plasma flow, or glomerular filtration rate.

In one patient with heart failure and in one without it, the increase in renal plasma flow was much greater than the increase in glomerular filtration rate, which indicated a considerable decrease in the filtration fraction towards normal in these two patients. In the others the filtration fraction was little changed although it was abnormally high in seven cases.

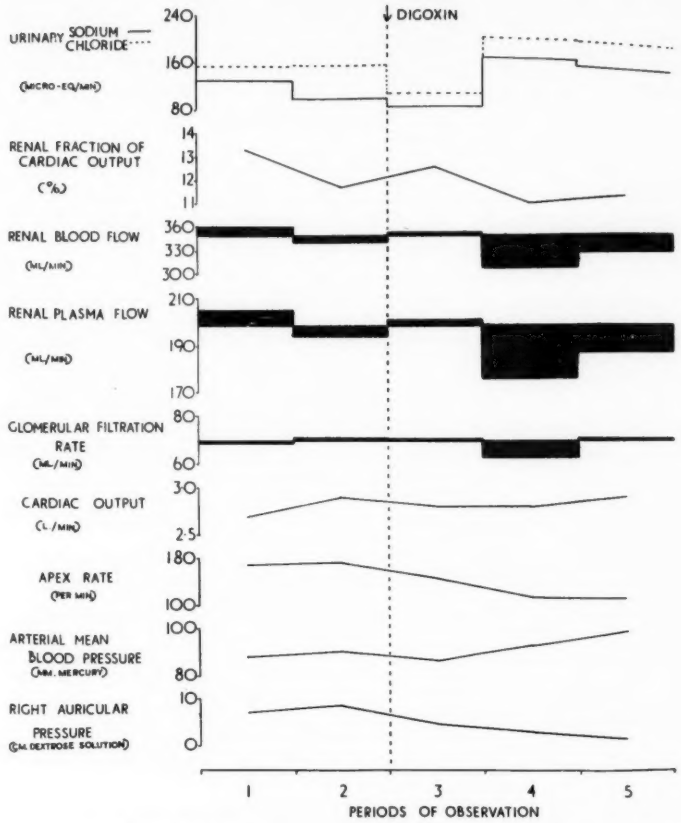

FIG. 2.—The effect of 1·5 mg. of intravenous digoxin on the systemic and renal circulations and salt excretion in Case 11.

The renal vascular resistances calculated from renal blood flow, arterial mean blood pressure, and right atrial pressure showed a fall in three patients with heart failure and in three without it. In one patient with heart failure and in two without it, there was an increase in renal vascular resistance, and in four patients, two with and two without congestive failure, little or no change.

In the patients with heart failure the renal fraction of the cardiac output, which was abnormally low in all except one, increased in one and fell or remained unaltered in the other five. In the patients without heart failure the drug was followed by an increase in the renal fraction of the cardiac output to a normal level in one, whereas in the others it remained abnormally low.

Changes in sodium and chloride excretion following digoxin. There was an increase in sodium and chloride excretion in three patients with heart failure and in six without this. In three patients the changes were small, the percentage increases being 33, 38, and 21 respectively, whereas in the other six, they were greater, the increases ranging from 57 per cent to 895 per cent. In two patients, one with and one without heart failure, there was little change in sodium and chloride excretion. In two patients with congestive failure, where the effect on chloride excretion was not studied, there was a 200 per cent increase in sodium excretion in one but no change in the other.

Discussion

Effect of intravenous digoxin upon cardiac output. In patients with clinical evidence of congestive heart failure in this series, the changes in cardiac output produced by intravenous digoxin were similar to those reported by McMichael and Sharpey-Schafer (1944), Howarth *et al.* (1947), Harvey *et al.* (1949), and Ferrer *et al.* (1950). Mitral stenosis was the dominant lesion in the three patients with the greatest increase in cardiac output (Fig. 1), whereas the patients showing a slight increase and no change in cardiac output after digoxin had severe mitral incompetence: it is possible that the mechanical defect of the incompetent valve prevented any increase in cardiac output. The resting cardiac output was high in the patient whose cardiac output fell after digoxin, and who had, in addition to mitral stenosis, extensive osteitis deformans. A high resting cardiac output has been described in patients with osteitis deformans by Edholm *et al* (1945), who also noted that this was lowered by digitalis, and by Howarth (1953).

In the patients with no clinical evidence of congestive heart failure the changes in cardiac output were in contrast to those observed in patients with congestive heart failure (Table and Fig. 2) and were more in keeping with the effects produced by digitalis in normal men (Stewart and Cohn, 1932; and Harvey *et al.*, 1949), and in dogs (Cohn and Steele, 1932).

Effect of intravenous digoxin upon heart rate, systemic blood pressure, and right auricular pressure. The changes in heart rate, systemic blood pressure, and right atrial pressure in this series are similar to those reported by Eichna and Taube (1944), McMichael and Sharpey-Schafer (1944), Wood and Paulett (1949) and Bayliss *et al.* (1950).

Digoxin produced its characteristic rapid and pronounced fall in heart rate in all the patients, with and without congestive heart failure (Table and Fig. 1 and 2). Generally there was an initial rise in the systolic blood pressure and, less consistently, in the diastolic pressure. The subsequent changes were variable, but the systolic pressure usually remained raised while there was little change in the diastolic pressure.

The right atrial pressure fell in all patients with congestive heart failure with the exception of one who had received digitalis until four days before the investigation: this patient must still have been under the influence of digitalis although not sufficiently to control the heart rate. The drug produced much smaller changes in right atrial pressure in patients without congestive heart failure, and a pronounced fall was observed in only one in whom the initial level was abnormally high (Table and Fig. 1 and 2).

Effects of intravenous digoxin upon the renal circulation. Using a technique similar to the present, Davies and Kilpatrick (1951) found that in normal subjects the renal plasma flow ranged from 540 to 817 ml. per minute, the glomerular filtration rate from 119 to 183 ml. per minute, the renal blood flow from 981 to 1483 ml. per minute, the filtration fraction from 0·18 to 0·30, and that the average for the renal fraction of the cardiac output was 22 per cent. All patients in the present series before intravenous digoxin showed an abnormally low renal plasma flow, the lowest values occurring in patients with congestive heart failure (Table). One patient without heart failure had a normal glomerular filtration rate initially, but all the others had low values. The reduction in renal plasma flow was greater than that in glomerular filtration rate and most patients had abnormally high filtration fractions. An abnormally low filtration fraction in a patient with congestive heart failure is an exceptional finding and in Case 3 was probably the result of renal involvement by polyarteritis nodosa. Unusually high figures for filtration fractions, such as occurred in Cases 4 and 5, have previously been reported by Davies and Kilpatrick (1951) in patients with congestive heart failure. After intravenous digoxin there was a large increase in renal plasma flow in three patients with heart failure and in two without this. This ranged from 20 to 115 per cent. In none of the remaining patients, where the change was always less than 11 per cent, was this considered significant (Fig. 2). The effects on renal plasma flow are similar to those observed by Farber *et al.* (1951), who found an increase in three out of ten patients with congestive heart failure, and Davison and Gaddie (1951), who noted an increase in four out of seven similar patients after giving

TABLE I

Effect of Intravenous Digoxin in Patients with Uncontrolled Auricular Fibrillation
(*a*) Before Digoxin. (*b*) 40 to 60 Minutes after Digoxin

TABLE I

EFFECT OF INTRAVENOUS DIGOXIN IN PATIENTS WITH UNCONTROLLED AURICULAR FIBRILLATION
(*a*) BEFORE DIGOXIN. (*b*) 40 TO 60 MINUTES AFTER DIGOXIN

Case number	Age (years) and sex	Diagnosis	Apex rate (per minute)	Systemic blood pressure range (mm. Hg)	Arterial mean blood pressure (mm. Hg)	Right atrial pressure (cm. 5% dextrose solution)	Cardiac output (l./min.)	Renal blood flow (ml./min.)	Renal fraction of cardiac output (percentage)	Renal plasma flow (ml./min.)	Glomerular filtration rate (ml./min.)	Filtration fraction	Systemic vascular resistance (dynes sec. cm.$^{-5}$)	Renal vascular resistance (dynes sec. cm.$^{-5}$)	Sodium excretion (micro. eq./min.)	Chloride excretion (micro. eq./min.)
A. Patients with congestive heart failure																
1	54 (F)	M.S.	(a) 140 to 176	130/90 to 150/110	113	+5 to +8·5	2·6	288	11·1	173	69	0·39	3470	28900	79	74
			(b) 106 to 112	135/90 to 150/115	116	−1 to +0·5	5·6	394	7·0	242	100	0·41	1630	22800	163	144
2	54 (M)	*M.S.	(a) 132 to 152	120/85 to 130/90	101	+6 to +8	11·3	470	4·2	296	85	0·29	716	15800	97	69
			(b) 92 to 106	135/90 to 145/100	111	+4 to +5	9·9	486	4·9	314	85	0·27	897	17100	129	105
3	53 (F)	*M.S.	(a) 138 to 160	170/110 to 210/120	137	+5·5 to +7	2·0	396	19·8	239	32	0·13	5480	25900	17	—
			(b) 84 to 88	185/100 to 210/110	135	0 to +2	2·6	525	20·0	316	47	0·15	4130	19900	51	—
4	42 (M)	M.S.	(a) 110 to 150	130/90 to 145/90	105	+4·5 to +9	2·75	192	7·1	112	75	0·67	3110	40200	9	—
		M.I.	(b) 90 to 108	145/90 to 150/100	112	+7 to +8	3·2	174	5·4	101	68	0·67	2810	47300	9	—
5	38 (F)	M.S.	(a) 166 to 174	135/90 to 140/90	103	+10 to +15	2·6	149	5·7	85	52	0·61	3170	48500	41	50
			(b) 80 to 86	140/80 to 145/85	103	+4 to +6	4·4	321	7·3	183	78	0·43	1875	23800	408	436
6	36 (F)	M.I.	(a) 118 to 124	130/75 to 135/80	96	+4 to +6	5·3	478	9·0	282	76	0·27	1450	14750	250	282
			(b) 72 to 74	105/50 to 135/80	74	−2·5 to +1	5·4	428	7·9	253	73	0·29	1095	13350	182	253
B. Patients without congestive heart failure																
7	46 (F)	M.I.	(a) 104 to 124	140/75 to 155/85	103	+0 to +3	6·2	640	10·3	390	141	0·36	1340	12250	232	240
			(b) 90 to 112	120/70 to 130/80	90	−4 to −1	6·7	675	10·1	419	136	0·32	1070	9650	364	364
8	67 (M)	*	(a) 112 to 130	135/80 to 140/90	109	−2 to −5	4·3	405	9·4	195	70	0·36	2020	21300	128	130
			(b) 90 to 112	130/80 to 140/80	98	−2 to −5	4·4	403	9·2	194	68	0·35	1765	19250	244	223
9	44 (F)	M.S.	(a) 116 to 136	120/75 to 135/95	99	+2 to +4	3·4	400	11·8	213	75	0·35	2320	18650	76	69
		M.I.	(b) 72 to 84	120/75 to 130/85	95	−2 to +2	2·8	530	19·0	292	79	0·27	2750	13800	201	149
10	46 (F)	M.S.	(a) 74 to 90	125/80 to 140/90	100	−1 to +1	4·0	420	10·5	253	87	0·34	1970	18350	162	164
			(b) 64 to 66	140/90 to 145/90	107	−2·5 to −1	4·0	464	11·6	272	98	0·36	2140	18000	170	138
11	35 (F)	M.S.	(a) 160 to 180	110/70 to 120/80	89	+7·5 to +8·5	2·8	350	12·5	199	70	0·35	2386	18450	115	156
			(b) 108 to 116	125/85 to 125/90	99	+1 to +2	2·9	328	11·3	187	71	0·38	2730	23000	159	201
12	41 (F)	*	(a) 140 to 180	120/75 to 130/90	98	−3 to +0·5	3·8	412	10·8	235	68	0·29	2060	18500	119	148
			(b) 80 to 100	110/70 to 130/80	88	−4 to −3	4·3	495	11·5	282	75	0·27	1635	13940	144	162
13	62 (M)	*	(a) 124 to 132	125/85 to 130/85	99	−6 to −3	4·3	583	13·6	280	117	0·42	1845	13600	167	142
			(b) 92 to 100	135/90 to 150/90	110	−7 to −4	4·9	523	10·8	257	117	0·46	1790	16800	279	208

* Case 2 had osteitis deformans as well, and Case 3, polyarteritis nodosa. In Case 8 no cause was discovered.
Cases 12 and 13 had thyrotoxicosis.

Discussion

Effect of intravenous digoxin upon cardiac output. In patients with clinical evidence of congestive heart failure in this series, the changes in cardiac output produced by intravenous digoxin were similar to those reported by McMichael and Sharpey-Schafer (1944), Howarth *et al.* (1947), Harvey *et al.* (1949), and Ferrer *et al.* (1950). Mitral stenosis was the dominant lesion in the three patients with the greatest increase in cardiac output (Fig. 1), whereas the patients showing a slight increase and no change in cardiac output after digoxin had severe mitral incompetence: it is possible that the mechanical defect of the incompetent valve prevented any increase in cardiac output. The resting cardiac output was high in the patient whose cardiac output fell after digoxin, and who had, in addition to mitral stenosis, extensive osteitis deformans. A high resting cardiac output has been described in patients with osteitis deformans by Edholm *et al* (1945), who also noted that this was lowered by digitalis, and by Howarth (1953).

In the patients with no clinical evidence of congestive heart failure the changes in cardiac output were in contrast to those observed in patients with congestive heart failure (Table and Fig. 2) and were more in keeping with the effects produced by digitalis in normal men (Stewart and Cohn, 1932; and Harvey *et al.*, 1949), and in dogs (Cohn and Steele, 1932).

Effect of intravenous digoxin upon heart rate, systemic blood pressure, and right auricular pressure. The changes in heart rate, systemic blood pressure, and right atrial pressure in this series are similar to those reported by Eichna and Taube (1944), McMichael and Sharpey-Schafer (1944), Wood and Paulett (1949) and Bayliss *et al.* (1950).

Digoxin produced its characteristic rapid and pronounced fall in heart rate in all the patients, with and without congestive heart failure (Table and Fig. 1 and 2). Generally there was an initial rise in the systolic blood pressure and, less consistently, in the diastolic pressure. The subsequent changes were variable, but the systolic pressure usually remained raised while there was little change in the diastolic pressure.

The right atrial pressure fell in all patients with congestive heart failure with the exception of one who had received digitalis until four days before the investigation: this patient must still have been under the influence of digitalis although not sufficiently to control the heart rate. The drug produced much smaller changes in right atrial pressure in patients without congestive heart failure, and a pronounced fall was observed in only one in whom the initial level was abnormally high (Table and Fig. 1 and 2).

Effects of intravenous digoxin upon the renal circulation. Using a technique similar to the present, Davies and Kilpatrick (1951) found that in normal subjects the renal plasma flow ranged from 540 to 817 ml. per minute, the glomerular filtration rate from 119 to 183 ml. per minute, the renal blood flow from 981 to 1483 ml. per minute, the filtration fraction from 0·18 to 0·30, and that the average for the renal fraction of the cardiac output was 22 per cent. All patients in the present series before intravenous digoxin showed an abnormally low renal plasma flow, the lowest values occurring in patients with congestive heart failure (Table). One patient without heart failure had a normal glomerular filtration rate initially, but all the others had low values. The reduction in renal plasma flow was greater than that in glomerular filtration rate and most patients had abnormally high filtration fractions. An abnormally low filtration fraction in a patient with congestive heart failure is an exceptional finding and in Case 3 was probably the result of renal involvement by polyarteritis nodosa. Unusually high figures for filtration fractions, such as occurred in Cases 4 and 5, have previously been reported by Davies and Kilpatrick (1951) in patients with congestive heart failure. After intravenous digoxin there was a large increase in renal plasma flow in three patients with heart failure and in two without this. This ranged from 20 to 115 per cent. In none of the remaining patients, where the change was always less than 11 per cent, was this considered significant (Fig. 2). The effects on renal plasma flow are similar to those observed by Farber *et al.* (1951), who found an increase in three out of ten patients with congestive heart failure, and Davison and Gaddie (1951), who noted an increase in four out of seven similar patients after giving

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(*a*) BEFORE DIGOXIN. (*b*) 40 TO 60 MINUTES AFTER DIGOXIN

Case number	Age (years) and sex	Diagnosis	Apex rate (per minute)	Systemic blood pressure range (mm. Hg)	Arterial mean blood pressure (mm. Hg)	Right atrial pressure (cm. 5% dextrose solution)	Cardiac output (l./min.)	Renal blood flow (ml./min.)	Renal fraction of cardiac output (percentage)	Renal plasma flow (ml./min.)	Glomerular filtration rate (ml./min.)	Filtration fraction	Systemic vascular resistance (dynes sec. cm.$^{-5}$)	Renal vascular resistance (dynes sec. cm.$^{-5}$)	Sodium excretion (micro. eq./min.)	Chloride excretion (micro. eq./min.)
A. Patients with congestive heart failure																
1	54 (F)	M.S.	(a) 140 to 176 (b) 106 to 112	130/90 to 150/110 135/90 to 150/115	113 116	+5 to +8·5 −1 to +0·5	2·6 5·6	288 394	11·1 7·0	173 242	69 100	0·39 0·41	3470 1630	28900 22800	79 163	74 144
2	54 (M)	*M.S.	(a) 132 to 152 (b) 92 to 106	120/85 to 130/90 135/90 to 145/100	101 111	+6 to +8 +4 to +5	11·3 9·9	470 486	4·2 4·9	296 314	85 85	0·29 0·27	716 897	15800 17100	97 129	69 105
3	53 (F)	*M.S.	(a) 138 to 160 (b) 84 to 88	170/110 to 210/120 185/100 to 210/110	137 135	+5·5 to +7 0 to +2	2·0 2·6	396 525	19·8 20·0	239 316	32 47	0·13 0·15	5480 4130	25900 19900	17 51	— —
4	42 (M)	M.S. M.I.	(a) 110 to 150 (b) 90 to 108	130/90 to 145/90 145/90 to 150/100	105 112	+4·5 to +9 +7 to +8	2·75 3·2	192 174	7·1 5·4	112 101	75 68	0·67 0·67	3110 2810	40200 47300	9 9	— —
5	38 (F)	M.S.	(a) 166 to 174 (b) 80 to 86	135/90 to 140/90 140/80 to 145/85	103 103	+10 to +15 +4 to +6	2·6 4·4	149 321	5·7 7·3	85 183	52 78	0·61 0·43	3170 1875	48500 23800	41 408	50 436
6	36 (F)	M.I.	(a) 118 to 124 (b) 72 to 74	130/75 to 135/80 105/50 to 135/80	96 74	+4 to +6 −2·5 to +1	5·3 5·4	478 428	9·0 7·9	282 253	76 73	0·27 0·29	1450 1095	14750 13350	250 182	282 253
B. Patients without congestive heart failure																
7	46 (F)	M.I.	(a) 104 to 124 (b) 90 to 112	140/75 to 155/85 120/70 to 130/80	103 90	+0 to +3 −4 to −1	6·2 6·7	640 675	10·3 10·1	390 419	141 136	0·36 0·32	1340 1070	12250 9650	232 364	240 364
8	67 (M)	*	(a) 112 to 130 (b) 90 to 112	135/80 to 140/90 130/80 to 140/80	109 98	−2 to −5 −2 to −5	4·3 4·4	405 403	9·4 9·2	195 194	70 68	0·36 0·35	2020 1765	21300 19250	128 244	130 223
9	44 (F)	M.S. M.I.	(a) 116 to 136 (b) 72 to 84	120/75 to 135/95 120/75 to 130/85	99 95	+2 to +4 −2 to +2	3·4 2·8	400 530	11·8 19·0	213 292	75 79	0·35 0·27	2320 2750	18650 13800	76 201	69 149
10	46 (F)	M.S.	(a) 74 to 90 (b) 64 to 66	125/80 to 140/90 140/90 to 145/90	100 107	−1 to +1 −2·5 to −1	4·0 4·0	420 464	10·5 11·6	253 272	87 98	0·34 0·36	1970 2140	18350 18000	162 170	164 138
11	35 (F)	M.S.	(a) 160 to 180 (b) 108 to 116	110/70 to 120/80 125/85 to 125/90	89 99	+7·5 to +8·5 +1 to +2	2·8 2·9	350 328	12·5 11·3	199 187	70 71	0·35 0·38	2386 2730	18450 23000	115 159	156 201
12	41 (F)	*	(a) 140 to 180 (b) 80 to 100	120/75 to 130/90 110/70 to 130/80	98 88	−3 to +0·5 −4 to −3	3·8 4·3	412 495	10·8 11·5	235 282	68 75	0·29 0·27	2060 1635	18500 13940	119 144	148 162
13	62 (M)	*	(a) 124 to 132 (b) 92 to 100	125/85 to 130/85 135/90 to 150/90	99 110	−6 to −3 −7 to −4	4·3 4·9	583 523	13·6 10·8	280 257	117 117	0·42 0·46	1845 1790	13600 16800	167 279	142 208

* Case 2 had osteitis deformans as well, and Case 3, polyarteritis nodosa. In Case 8 no cause was discovered.
Cases 12 and 13 had thyrotoxicosis.

intravenous digoxin. Since renal plasma flow is directly related to renal blood flow, the present results indicate that intravenous digoxin sometimes increases renal blood flow when given to patients with uncontrolled auricular fibrillation, with or without congestive heart failure.

An abnormally high renal venous pressure has been considered as a possible factor responsible for a low renal blood flow in patients with congestive heart failure and the fall in systemic venous pressure as a cause for the increase in renal blood flow following intravenous digoxin. There is, however, little support for the view that a high renal venous pressure is the primary cause of an abnormally low renal blood flow in patients with congestive heart failure. Merrill (1946) failed to find any correlation between the depression of renal function and the height of the systemic venous or right atrial pressure in patients with congestive heart failure. Blake *et al.* (1949) noted that elevation of the renal venous pressure above 35 cm. of saline reduced both renal plasma flow and glomerular filtration rate in dogs, but observed no effect from lower pressures, comparable to those usually present in patients with congestive heart failure. Seymour *et al.* (1942) considered that the reduction in renal blood flow in patients with congestive heart failure was proportional to the fall in cardiac output, but thought that a high renal venous pressure produced an abnormally high glomerular capillary pressure and increased the filtration fraction. Davison and Gaddie (1951) studied the effect on renal function of lowering the systemic venous pressure by venous occlusion of the thighs in patients with congestive heart failure, and found that reduction of systemic venous pressure produced no effect on renal plasma flow or glomerular filtration rate. The right atrial pressure fell in five patients with congestive heart failure in this series, but the renal blood flow increased in only three of these, where there was also a large increase in cardiac output (Fig. 1) and remained unaltered in the other two where the cardiac output did not rise. In those without heart failure the right atrial pressure fell in five, but the renal blood flow increased in only two and did not rise in the patient with the most dramatic fall in right atrial pressure (Fig. 2). These findings support those of Merrill (1946) and Davison and Gaddie (1951) and show that abnormalities in renal function in patients with congestive heart failure are not directly related to elevation of renal venous pressure. In Case 5, however, where the right atrial pressure was initially much higher than in any of the others and where intravenous digoxin caused an increase in renal blood flow out of proportion to the increase in cardiac output, it is possible that renal venous pressure was having a direct effect on renal blood flow.

All three patients with congestive heart failure who showed an increase in cardiac output, which was accompanied by an increase in renal blood flow and renal plasma flow, also had a marked increase in glomerular filtration rate following intravenous digoxin (Fig. 1). In two of these, the increase in glomerular filtration rate was proportional to that in renal plasma flow and there was little change in filtration fraction. In the other, where the renal plasma flow increased relatively more than the glomerular filtration rate and the filtration fraction fell, the extremely high renal venous pressure before treatment may have been making an active contribution to glomerular filtration as suggested by Seymour *et al.* (1942). Intravenous digoxin caused no significant change in glomerular filtration rate in any of the other patients (Fig. 2) and there was little change in filtration fraction except in Case 9, where an increase in renal blood flow was associated with a much smaller increase in glomerular filtration rate.

These results indicated that the changes in renal blood flow, which followed the administration of intravenous digoxin to patients with uncontrolled auricular fibrillation and congestive failure, closely paralleled the changes in cardiac output and were not directly related to lowering of the renal venous pressure. The changes in renal blood flow were reflected in similar changes in renal plasma flow and glomerular filtration rate. In patients with uncontrolled auricular fibrillation without congestive failure intravenous digoxin occasionally produced an increase in renal blood flow unaccompanied by a similar change in glomerular filtration rate.

Effect of intravenous digoxin upon systemic and renal vascular resistances and the renal fraction of the cardiac output. In the patients with congestive failure the systemic vascular resistance fell in five and in four of these the renal vascular resistance also fell. In one in whom the initial right

atrial pressure was very high, the renal vascular resistance fell proportionately more than the systemic vascular resistance and the renal fraction of the cardiac output increased. In Cases 1 and 6 the fall in systemic was proportionately greater than that in renal vascular resistance and the renal fraction of the cardiac output decreased. In Case 3 the systemic and renal vascular resistances were similarly affected and there was no change in the renal fraction of the cardiac output. Although the systemic vascular resistance fell in Case 4, the renal vascular resistance rose and the renal fraction of the cardiac output was less after intravenous digoxin. Both systemic and renal vascular resistances increased in Case 2 and there was a slight fall in the renal fraction of the cardiac output. These findings are similar to those of Eichna *et al.* (1951) and show that, in most patients with uncontrolled auricular fibrillation and congestive heart failure, intravenous digoxin causes a fall in total peripheral vascular resistance which affects the renal vascular resistance less than that elsewhere. The fall in total peripheral resistance is probably a reflex baroceptor response since Ead *et al.* (1952) and Sharpey-Schafer (1953) showed that an increase in pulse pressure, such as follows intravenous digoxin, causes peripheral vasodilatation.

In the patients without congestive heart failure, the systemic and renal vascular resistances decreased proportionately in three, and the renal fraction of the cardiac output was unaltered. In one there was no significant change in either vascular resistance; in one the systemic and renal vascular resistance increased and in both of these patients the renal fraction of the cardiac output was unaltered. In Case 13 the systemic vascular resistance remained the same but the renal vascular resistance increased and the renal fraction of the cardiac output fell. In Case 9 there was a large increase in the renal fraction of the cardiac output after digoxin, since the renal vascular resistance fell while the systemic vascular resistance rose. These results show that the effects of intravenous digoxin upon peripheral vascular resistance are less consistent in patients with uncontrolled auricular fibrillation without heart failure than in similar patients with heart failure, and suggest that digitalis has no direct effect on the peripheral circulation and no immediate action in restoring a normal distribution of blood to the kidneys.

Effect of intravenous digoxin upon sodium and chloride excretion. There was a marked increase in salt excretion in three patients with and in four without congestive heart failure. A slight but smaller increase also occurred in one with and in two without heart failure. The patients with heart failure in whom there was a marked increase in salt excretion were the only ones showing a significant rise in cardiac output, renal blood flow, renal plasma flow, and glomerular filtration rate, and the enhanced excretion was probably due to the larger tubular load (Fig. 1). The increase in tubular load would also be more than sufficient to produce the changes seen in Cases 9, 11, and 12 (Fig. 2), but in Cases 2, 7, 8, and 13 no alteration in tubular load was apparent to account for the rise in salt excretion. In one this was within the limits of physiological variation demonstrated by Stanbury and Thomson (1951) in normal subjects, but in the other three where the increases in salt excretion were greater, digoxin may have directly depressed tubular reabsorption of salt, although the enhanced excretion could have been produced entirely by a change in tubular load too small to be apparent from the method of estimating glomerular filtration rate. Farber *et al.* (1951), and Eichna *et al.* (1951) also thought that digoxin directly affected salt excretion by decreasing tubular reabsorption.

All the patients in the present investigation were given 500 ml. of water to ensure adequate urine flows and it was impossible to assess accurately the diuretic effect of intravenous digoxin, because of the possibility of an associated water diuresis. However, in all the patients in whom there was much increase in salt excretion, there was also a sustained water diuresis.

Summary

Changes in systemic and renal circulations and salt excretion following a single intravenous injection of digoxin were studied in thirteen patients with uncontrolled auricular fibrillation, of whom six had congestive heart failure.

The heart rate decreased in all thirteen patients. The cardiac output increased in four patients with congestive heart failure, was unchanged in one, and decreased in the other. Much smaller changes occurred in those without heart failure.

In most patients there was an initial rise in systolic blood pressure and, less consistently, in diastolic pressure. The subsequent changes were variable, but the systolic pressure usually remained raised while there was little change in the diastolic pressure.

In five patients with heart failure the right atrial pressure decreased and in the other it remained unchanged. Only one patient without heart failure showed much fall in right atrial pressure and she had an unusually high initial level.

Before digoxin all thirteen patients had abnormally low renal blood flows and renal plasma flows and all but one patient, without heart failure, had low glomerular filtration rates. The smallest values were seen in those with heart failure. After digoxin there was an increase in renal blood flow, renal plasma flow, and glomerular filtration rate in three of four patients with heart failure who showed an increase in cardiac output. In two without heart failure there was an increase in renal blood flow and renal plasma flow which was independent of an increase in cardiac output and was unaccompanied by a similar change in glomerular filtration rate. In the other eight there was little or no change in renal circulation.

In most patients changes in renal plasma flow and glomerular filtration rate were unaccompanied by alterations in filtration fractions, which remained abnormally high.

The systemic vascular resistance fell in all except one patient with congestive heart failure, but no consistent changes occurred in those without heart failure. Digoxin did not appear to have any direct effect on peripheral vascular resistance since the changes observed in those with heart failure were probably due to a reflex baroceptor response. There were no uniform changes in the renal vascular resistance.

Although the renal fraction of the cardiac output was initially abnormally low in most patients, digoxin produced no consistent change in this fraction, and appeared to have no immediate effect in restoring a normal distribution of blood to the kidneys.

There was a large increase in salt excretion in all three patients with congestive heart failure who showed a rise in cardiac output, renal blood flow, renal plasma flow, and glomerular filtration rate. This increase in salt excretion was probably caused by an improvement in renal circulation following the rise in cardiac output. There was, however, an increase in salt excretion in some others where there was no evidence of a change in the tubular load, suggesting that digoxin also had a direct effect on tubular reabsorption of salt.

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VENTRICULAR EXTENSION INTO THE ABDOMINAL WALL

BY

CLIFFORD PARSONS

From the Birmingham Children's Hospital

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In a previous paper mention was made of a girl with cyanotic congenital heart disease and a pulsatile tumour under the umbilicus (Astley and Parsons, 1953). This child died in Birmingham Children's Hospital in 1950, but the condition was thought to be a chance monstrosity until 1952, when Dr. Helen Taussig referred in a letter to another example of this condition. In 1955 both Dr. Catherine Neill and Dr. James Brown drew my attention to descriptions of other similar cases.

Case Report

M. A., the fifth child of a healthy family, was born after a pregnancy complicated by a small hæmorrhage at the third month. A pulsating swelling at the umbilicus was noticed at birth; intermittent cyanosis was first observed six months later. Cyanotic attacks became increasingly severe and frequent, especially when feeding or crying, and she was unconscious when, at the age of 18 months, she was admitted to hospital for the last time in one of these attacks. She was quite well-developed, and uniformly cyanosed, with moderate clubbing of fingers and toes (hæmoglobin, 14·7 g.; red blood corpuscles, 6·8 million). The venous pressure was raised, the liver enlarged, and the lungs slightly congested. Arterial pulses were normal, and the blood pressure in the arms 120/?100 mm. Apical impulses could be felt in the fourth left intercostal space just internal to the mid-clavicular line, and in the fifth right space in the mid-clavicular line; the chest was not deformed. A systolic thrill was felt at the right sternal margin in the second and third spaces and a harsh systolic murmur was heard all over the front of the chest, and faintly between the scapulæ. A systolic thrill and a continuous murmur could be detected over a smoothly-rounded, pulsatile swelling immediately deep to the umbilicus. A straight cord, which also pulsated, ran under the skin between the epigastric notch and the upper border of the tumour. The depth of cyanosis was not affected by compressing the tumour or its connections. X-ray examination supported a diagnosis of dextrocardia, but an electrocardiogram, using only the standard limb leads, showed peaked P waves in lead II, marked left axis deviation, and rather wide ventricular complexes, suggesting the possibility of tricuspid atresia with a diminutive right ventricle. No further investigations were possible until after death, when radio-opaque material injected into the superior vena cava demonstrated a communication between right and left atria, and outlined the pulmonary veins. An injection into the sub-umbilical tumour showed connections with the aorta and its branches through a ventricle.

Necropsy. The only abnormalities were those related to the heart. Externally (Fig. 1) the aorta and pulmonary artery appeared to arise from two ventricles separated by an interventricular groove; the right atrium was dilated. The apex of the heart was fusiform and continued downward as a muscular tube " like an anteater's snout " to an ovoid tumour (27 × 18 × 10 mm.) lying deep to the umbilicus. Unfortunately the reflections of the pericardium were not adequately examined, but a membrane attached to the front of the tube in its upper part was presumably the anterior mesocardium.

Dissection confirmed that the right atrium was large, receiving both venæ cavæ and the pulmonary veins from the right lung. It did not communicate with the right ventricle but opened into the left atrium through a high septal defect. No ridge in the roof marked the position of the septum secundum and the division between the atria; the lower part of the interatrial septum was intact. The left atrium was somewhat smaller than the right, receiving the left pulmonary veins and emptying through a normal bicuspid mitral valve into an enormously hypertrophied left ventricle, with a wall 17 mm. thick. The aorta was 32 mm. in circumference at its ostium, and the aortic valve, coronary arteries, aortic arch and its branches

were all normal and the ductus arteriosus was closed. The right ventricle was represented by a thin-walled narrow tube, 7 mm. in circumference and with a smooth internal surface, lying on the surface of the left ventricle adjacent to the interventricular groove (Fig. 2). This tube opened through a bicuspid pulmonary

FIG. 1.—Complete specimen. The skin of the umbilicus can be seen at the bottom of the illustration and the ventricular extension is a little to the right of the mid line.

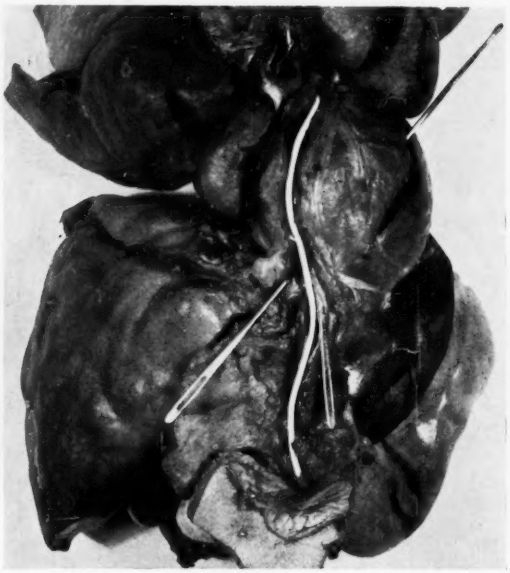

FIG. 2.—Specimen opened. The white marker runs through the ventricular extension and right ventricle into the pulmonary artery; the vertical probe runs from the ventricular extension through the left ventricle into the aorta; the oblique probe runs through the interventricular septal defect.

valve into a pulmonary artery which was normally distributed but hypoplastic (circumference 16 mm.). A channel 3 mm. in diameter led from left to right ventricle through the muscular septum. A rudimentary valve, with two chordæ tendineæ but no cusps, guarded its opening into the right ventricle. Another narrow channel connected the extreme apex of the left ventricle with the lower end of the right ventricle (Fig. 3). An extension of the right ventricle formed a muscular tube leading to what looked like a third ventricle, a muscular chamber with a trabeculated inner surface (Fig. 4). In this structure also myocardial fibres were hypertrophied, and there was interstitial fibrosis. The endocardium was thickened and fibrotic.

DISCUSSION

Formijne (1950) observed a somewhat similar condition in a 30-year-old woman who died during thoracotomy. She was found to have two superior venæ cavæ, tricuspid atresia, a wide atrial septal defect, a small ventricular septal defect and a rudimentary right ventricle. The " trunk-like " prolongation towards the umbilicus was an extension of the *left* ventricle. This was true, also, of a male infant described by Snellen *et al.* (1952). In this case there was a persistent anterior mesocardium and a high ventricular septal defect. All four chambers were enlarged; the right ventricle being larger than the left, and the pulmonary artery larger than the aorta. This patient had been fully investigated during life, angiocardiograms were taken and catheterization performed. The physical signs and X-ray findings were much the same as in those described in the present case, but an electrocardiogram showed right ventricular preponderance.

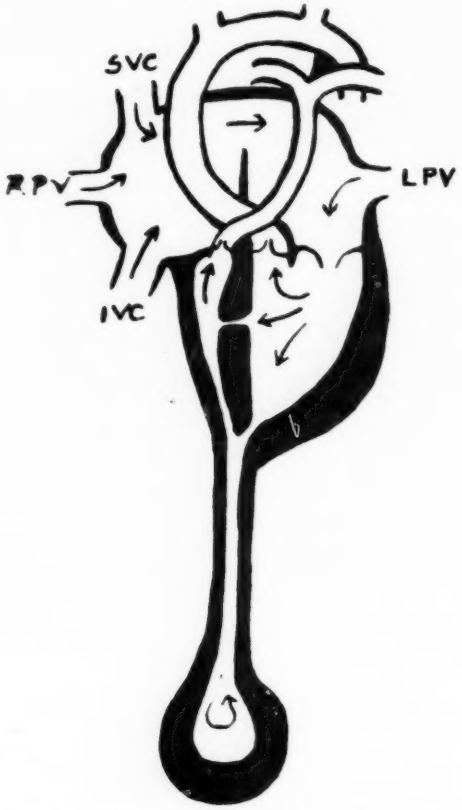

FIG. 3.—Diagrammatic representation of the anomaly.

There is a sufficient similarity between these three cases to suggest a common defect in development. The heart develops in the neck and migrates to the thorax in close association with the septum transversum, which forms a diaphragm separating the heart from the abdominal cavity and the yolk sac. The separation becomes still more marked when, in the seventh week, the rapidly growing liver bulges forward and interposes an even thicker layer between the heart and the stalk of the yolk sac, which by now is being incorporated into the umbilical cord. If, therefore, the elongated diverticulum characteristic of these three cases is due to the developing heart being caught up in the umbilical structures, the defect must occur very early in embryonic life.

In the fourth week the cardiac tube is elongating rapidly and, as it is fixed at both ends, it forms a loop. It lies in the splanchnic mesoderm—into which the liver is just beginning to grow—and, because the embryo is acutely flexed, the apex of this ventricular loop presses against the yolk sac. If the heart wall were to become attached to the structures of the yolk sac at this stage, the ventricular loop would be drawn out in front of the rapidly growing liver as the embryo straightened. The diverticulum so formed might be made up of tissue needed for the normal development of either ventricle, and in consequence that chamber would be deformed. In turn this might influence the development of the atrio-ventricular canal—contributing in our patient to the tricuspid valve deformity, and so to the maintenance of an interatrial communication.

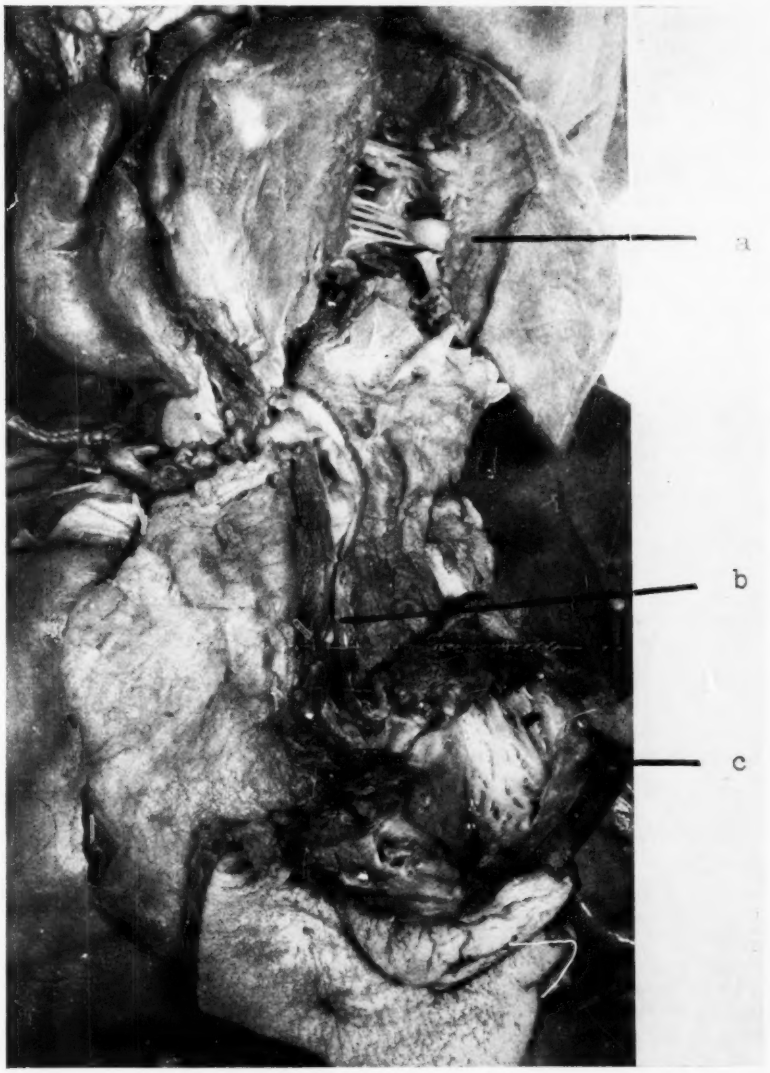

FIG. 4.—Close-up view of left ventricle (a), the ventricular extension (b), and interior of the sub-umbilical chamber (c).

There is another reason for assuming that arrest of development occurred at about the fourth week. Early in the life of the embryo the endothelial tubes that form the heart and the gut are enfolded by the splanchnic mesoderm, giving to the heart, the gut, and later the liver, a dorsal and a ventral mesentery. The hepatic ventral mesentery persists as the falciform ligament. The intestinal ventral mesentery quickly disappears (except where it is attached to the foregut on the cranial side of the yolk sac) and in embryos 2 mm. long both dorsal and ventral mesocardia have

also disappeared and the heart already lies free in the pericardium. It follows that persistence of a ventral mesocardium is indicative of a defect occurring before the end of the fourth week. Snellen *et al.* (1952) carefully studied the pericardial reflections in their case and demonstrated prolongations of the pericardial cavity, one lying behind and one on either side of the muscular tube. The anterior surface of the myocardial tube was not covered by pericardium, but a ventral mesocardium was clearly recognized. It was probably present in our case also.

Summary

A rare developmental anomaly of the heart is described. It consisted of tricuspid atresia, atrial septal defect, abnormal drainage of the right pulmonary veins, hypertrophied left ventricle, diminutive right ventricle, hypoplastic pulmonary artery, and a tubular extension of the right ventricle lying in the anterior abdominal wall. Reasons are given for thinking that it arose during the fourth week of fœtal life.

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BAROCEPTOR RESPONSES TO ACUTE RHYTHM CHANGES

BY

SHEILA HOWARTH* AND E. P. SHARPEY-SCHAFER

From the Department of Medicine, St. Thomas' Hospital

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There is now evidence that the response of the peripheral resistance to acute changes in the stroke output of the heart is determined by baroceptor reflexes, since it has been shown in cats (Ead *et al.*, 1952) and in man (Sharpey-Schafer, 1953) that these receptors respond to arterial pulse pressure as well as mean pressure changes. In normal man when the effective filling pressure of the heart is reduced by the Valsalva manœuvre or the erect posture, the subsequent decrease in stroke output and arterial pulse pressure is followed by peripheral vasoconstriction. It is more difficult to increase suddenly the normal stroke output and pulse pressure; but it has been shown that imposed cough transients are followed by peripheral vasodilatation (Sharpey-Schafer, 1953), which also results from the increased pulse pressure during squatting (Sharpey-Schafer, 1956).

It seemed possible that spontaneous acute changes in cardiac rhythm might provide additional evidence, since pulse pressure may alter conspicuously with sudden slowing or quickening of the heart beat.

Material and Methods

Two groups of cases were studied. In the first group, seven cases of paroxysmal tachycardia or flutter were chosen for short frequent bursts of ectopic rhythm occurring in an otherwise normal heart. A second commoner group of seventeen cases with heart disease and heart failure were also studied.

Intravascular pressures were recorded with capacitance manometers and forearm flow with the venous occlusion plethysmograph.

Results

Group I

Effects of Sudden Slowing. Continuous arterial records during the change from a fast ectopic rhythm to sinus rhythm were obtained in five cases. The results were the same in all. The pulse pressure of the first normal beat was greatly increased when compared with the pulse pressure during the ectopic rhythm and the mean pressure of this beat was unaltered. Thereafter, however, diastolic and mean pressure decreased over three or four beats (Fig. 1). In two patients forearm flow was measured before and directly after the change to sinus rhythm. The flows after the change to sinus rhythm were 2·4 and 2·9 times respectively the flows before the rhythm change. The decrease in mean arterial pressure and increase in forearm flow indicate vasodilatation.

Effects of Sudden Rapid Beating. The onset of an ectopic rhythm was recorded four times, with similar results in all. There was an immediate and conspicuous decrease in pulse pressure. Mean pressure either remained constant or after a few beats began to fall slightly. After about fifteen beats of the rapid rhythm, however, mean pressure rose indicating the onset of vasoconstriction (Fig. 2).

* Formerly Senior Research Fellow, Institute of Cardiology.

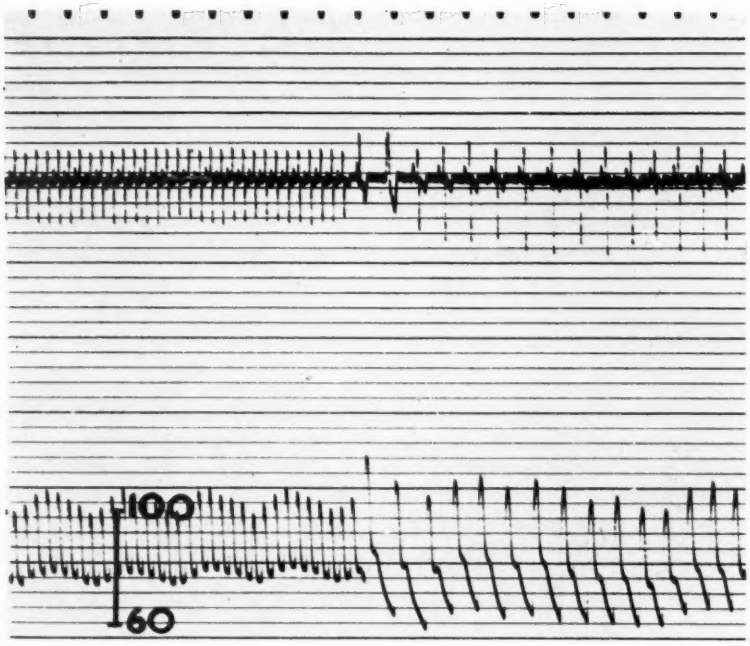

FIG. 1.—Upper trace electrocardiogram. Lower trace arterial pressure. Time marker in seconds and calibration in mm. Hg in this and subsequent figures. The increased pulse pressure with the change to sinus rhythm caused vasodilatation and a fall in mean arterial pressure.

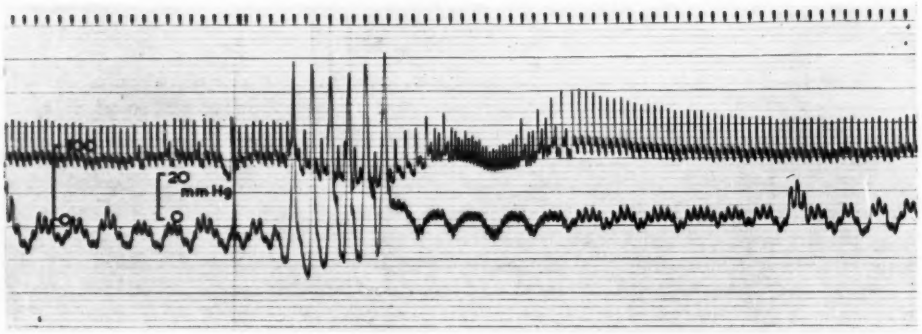

FIG. 2.—Upper trace arterial pressure. Lower trace intrathoracic (œsophageal) pressure. Three seconds after 6 cough transients there was a burst of fast ectopic rhythm. After a further 5 seconds the rise in mean arterial pressure indicates the onset of vasoconstriction.

Acute Rhythm Change under a Sympathetic Blocking Agent. Fig. 3 shows a record from a patient who was known to have paroxysmal tachycardia, but whose circulation was otherwise normal. In the course of a surgical procedure 50 mg. of hexamethonium were given intravenously and the record obtained shortly after. It will be seen that in spite of a conspicuous decrease in pulse pressure with onset of the ectopic rhythm there is no evidence of vasoconstriction. The change back to sinus rhythm was also recorded and showed no evidence of vasodilatation.

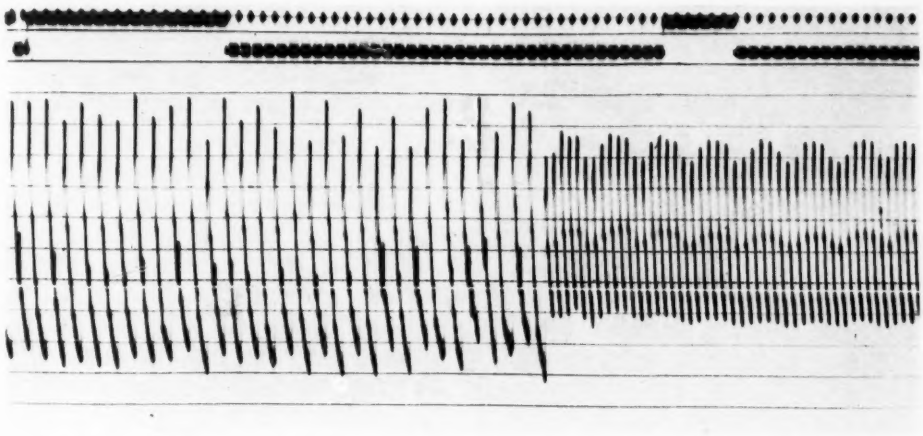

FIG. 3.—Arterial pressure curve. Hexamethonium, 50 mg., had been given a few minutes previously. Spontaneous change to a fast ectopic rhythm did not cause changes in mean arterial pressure.

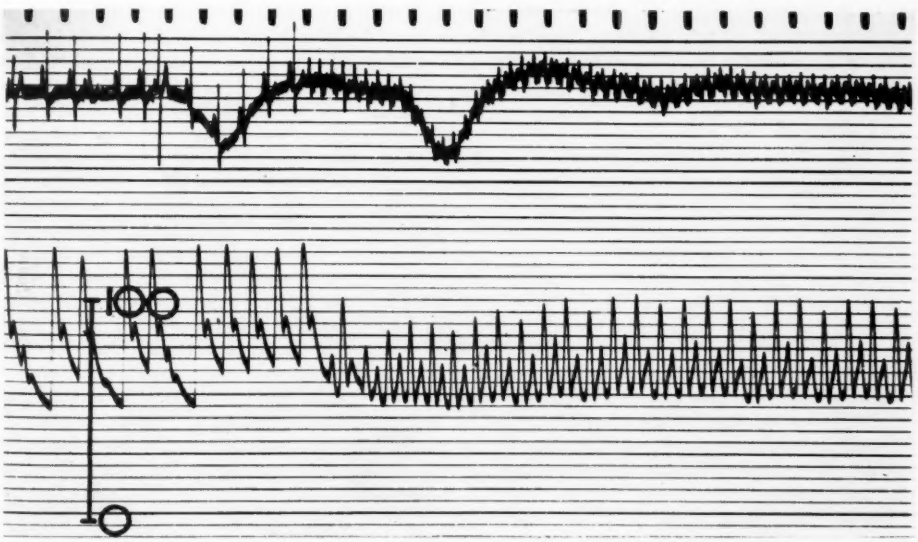

FIG. 4.—Upper trace electrocardiogram. Lower trace arterial pressure. With the change to a fast ectopic rhythm there was a fall in mean pressure and gross pulsus alternans. Rheumatic heart disease and heart failure.

Group II

Acute Rhythm Changes in Heart Failure. Thirty-eight records were obtained in cases with heart failure. In continuous arterial records, conspicuous output changes often largely obscured baroceptor constriction or dilatation. Thus the onset of a rapid rhythm decreased minute output to such an extent that arterial mean pressure fell (Fig. 4), the changes being reversed on return to sinus rhythm (Fig. 5). Forearm flows were recorded in three cases where mean arterial pressure changes

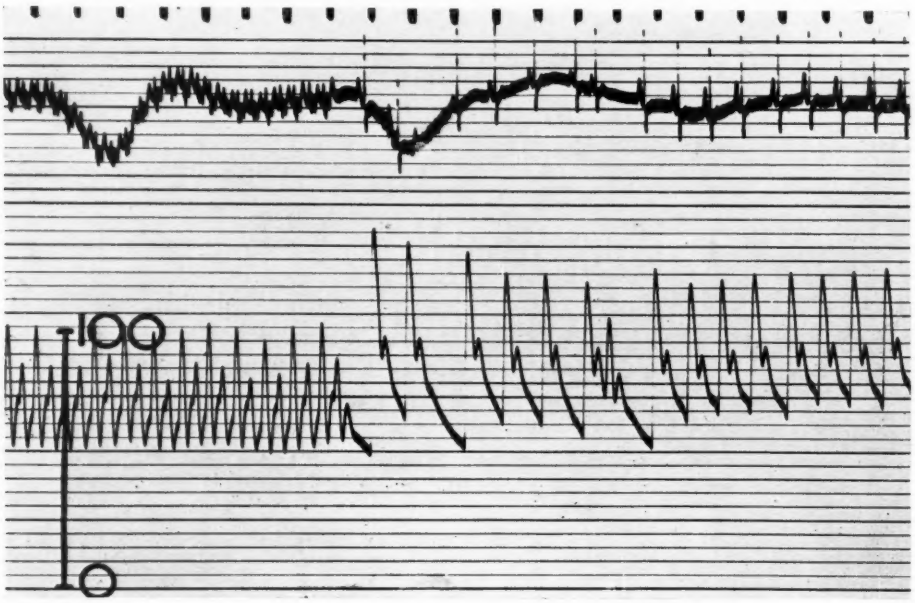

FIG. 5.—The same case as in Fig. 4, showing change back to sinus rhythm. See text.

were small. There was a great decrease in flow during the ectopic rhythm indicating vasoconstriction. In Fig. 5 it will be seen that arterial pressure is highest the moment sinus rhythm is established; thereafter it falls off as peripheral dilatation occurs in response to the increased pulse pressure.

In the most severe cases blood flow virtually ceased and arterial pressure fell rapidly below syncopal levels (Fig. 6). Death follows if the rhythm persists. In short attacks, however, the picture is that of a Stokes-Adams attack, except that the heart rate is rapid. With return to sinus rhythm there is an " overshoot " in arterial pressure similar to the " overshoot " that follows a Stokes-Adams attack (Barlow and Howarth, 1953) and indicates constriction during the attack itself.

DISCUSSION

The results are consistent with the general theory of baroceptor responses to acute pulse pressure changes. When the first large beat occurs following the cessation of an ectopic rhythm the peripheral resistance is determined by the pulse pressure during the ectopic rhythm, and the mean pressure of this beat is unaltered. This beat, however, stimulates the baroceptors and by the time of the next beat there is demonstrable vasodilatation. Thereafter a new level of peripheral resistance is progressively established. This response to a single large beat is similar to the vasodilatation which can be demonstrated following a single cough transient (Sharpey-Schafer, 1953).

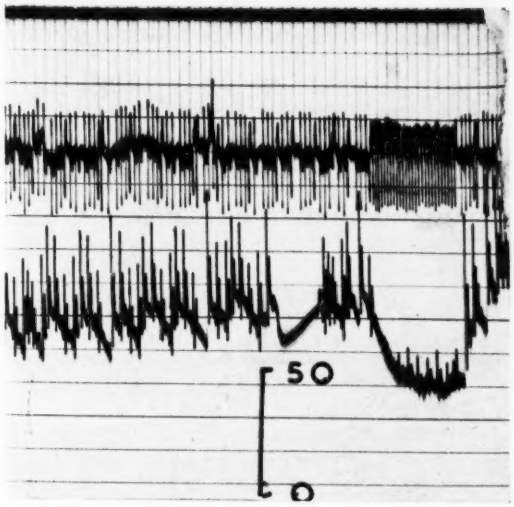

FIG. 6.—Upper trace electrocardiogram. Lower trace arterial pressure. A burst of ectopic rhythm (rate about 200 per minute) caused an acute decrease in arterial pressure and syncope. The interruption in the arterial record seen above the calibration was due to washing through the needle.

The onset of vasoconstriction with sudden decrease in pulse pressure has a rather different time relationship. In the absence of afferent impulses, the vasomotor centre is thought to exert a high level of vasoconstriction. Under normal conditions bursts of afferent impulses with each heart beat inhibit the vasomotor centre to a degree which is represented by the normal peripheral vascular resistance. Sudden increase in pulse pressure increases the inhibitory impulses and as shown above vasodilatation can be demonstrated after one such beat. Sudden decrease in pulse pressure decreases the number of afferent impulses, but the system takes time to respond. Thus there is a delay of a few seconds before constriction can be shown, and a single small beat is without demonstrable effect. This delay in the onset of constriction has been observed in other conditions: during the Valsalva manœuvre, in normal subjects, constriction does not appear for five or six seconds (Sharpey-Schafer, 1955) and on standing erect after squatting there is a similar delay (Howard *et al.*, 1951).

The records of rhythm changes obtained under hexamethonium are those expected since the drug blocks baroceptor reflexes on the efferent pathway.

The effects of acute ectopic rhythms on the failing circulation are similar, but gross output changes largely obscure the baroceptor response in arterial records. That flutter and paroxysmal tachycardia cause intense constriction in such cases has long been known on clinical grounds. For if the abnormal rhythm persists more than a few minutes the limbs and the tip of the nose become cold and the skin cyanotic, while a conspicuous rise of venous pressure is immediate.

When stroke output falls to the lowest levels and baroceptor constriction is unable to maintain arterial pressure above 50 mm. Hg, syncope results.

SUMMARY

The onset and cessation of fast ectopic rhythms was studied by continuous arterial records. When the heart slowed suddenly the first large beat was followed by a fall in mean arterial pressure

and increase in forearm blood flow indicating vasodilatation. When the heart quickened suddenly and pulse pressure decreased, mean arterial pressure rose and forearm blood flow decreased indicating vasoconstriction.

A case with a spontaneous rhythm and pulse pressure change under a sympathetic blocking agent showed no change in mean arterial pressure.

The results are compatible with the general theory of baroceptor responses to acute pulse pressure changes.

In diseased failing hearts, minute output changes with ectopic rhythms may obscure changes of peripheral resistance in continuous arterial records. Thus a fast rhythm may reduce cardiac output and arterial pressure to syncopal levels.

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ADRENALINE SENSITIVITY OF PERIPHERAL BLOOD VESSELS IN HUMAN HYPERTENSION

BY

ROBERT S. DUFF

From the Cardiological Department, St. Bartholomew's Hospital

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The exact cause of the increased peripheral resistance in chronic arterial hypertension is unknown. It is not due to generalized overactivity of the vasomotor nerves for Prinzmetal and Wilson (1936), Pickering (1936*a*), and Stead and Kunkel (1940) showed that the vasoconstriction responsible for essential hypertension is not neurogenic. Search for abnormal pressor agents in the blood stream has generally been unsuccessful (Hülse, 1924: Aitken and Wilson, 1935; Pickering, 1936*b*). Likewise, with rare exceptions such as phæochromocytoma, no increase in the level of naturally occurring pressor hormones has been found (Engel and von Euler, 1950; Raab and Gigee, 1954). Organic narrowing of the arterioles cannot be responsible, for this occurs only in the later stages and in restricted portions of the vasculature (Moritz and Oldt, 1935).

There remains, however, one further possibility of accounting for the generalized reduction of peripheral vascular calibre in hypertension: increased sensitivity of the terminal arterioles to normal constrictor stimuli. The present paper describes a method of selectively measuring the sensitivity of blood vessels and submits observations on groups of subjects with normal and raised blood pressures, respectively.

SUBJECTS

Findings in 39 subjects with normal blood pressures (under 150/90 mm. Hg) have been contrasted with those of 25 hypertensive patients. The normals were mostly healthy medical student volunteers but included some patients with non-hypertensive disorders of the circulation, such as Raynaud's disease. Their ages ranged from 20 to 51 years.

Only patients with persistent elevation of blood pressure over 200/100 mm. Hg were included in the hypertensive group. After clinical, electrocardiographic and radiological assessment each case was graded according to the condition of the heart, retinæ, coronaries, and kidneys:

(*a*) benign—when these structures were affected but little or not at all;

(*b*) progressive—when one or more tissue had severe or perceptibly increasing damage; or

(*c*) malignant—when papilloedema associated with gross vascular lesions were present.

Important characteristics of the various groups of subjects are summarized in Table I.

TABLE I

SUBJECTS

Group	Men	Women	All	Mean age
With normal pressure	30	9	39	29
With raised pressure	7	18	25	50

Methods

Throughout each test the subject reclined comfortably on a couch in a room maintained at a temperature of $23 \pm 1^{\circ}$ C. At regular half-minute intervals the blood flow in both hands was measured separately by venous occlusion plethysmography, following a standard procedure (Duff, 1952).

Under local anæsthesia a continuous infusion into the brachial artery on one side was set up, using a power-driven double-channel apparatus delivering saline at a constant rate. At regular 4-minute intervals plain saline (0·9% (w/v) NaCl solution) was alternated with solutions of adrenaline sufficiently diluted to ensure minimal responses confined to the infused hand. Each solution was freshly prepared by adding synthetic L-adrenaline tartrate (B.D.H.) to saline containing a trace of ascorbic acid to prevent catechol deterioration. Every subject was tested with two or more of the following adrenaline concentrations: 1/64, 1/16 and 1/8 μg./min. The highest dose used was therefore less than 5 per cent of that required systemically to cause either subjective symptoms or perceptible effects on heart or blood pressure. Under these conditions subjects generally were comfortable throughout the period of observation, and remained unaware of the infusions.

Independent measurements of the blood flow in the test hand and in the opposite control hand are obtained while a continuous infusion is given into the brachial artery on the test (usually the right) side. When saline alone is being infused the variation in blood flow on one side during a given period is approximately the same as that on the other side, but when an effective amount of adrenaline is added, this close parallelism is disturbed by the resulting vasoconstriction in the test hand. If A and B are the mean blood flows in the test hand during successive periods of time and a and b are corresponding values for the other hand, then A/B approximately equals a/b. When three of these values are known the fourth can be calculated: e.g. $B = Ab/a$. If saline alone is infused during the first period (corresponding blood flows in the two hands averaging A and a) and adrenaline is added during the second period (corresponding blood flows being B and b), then an estimate E of what the blood flow in the test hand would have been *had the adrenaline been ineffective* is obtained by $E = Ab/a$. Therefore the net effect of the adrenaline is the difference between the observed mean B and the expected mean E, after due allowance for experimental error. When the observed mean B is less than the calculated mean E (derived from three observed control means) it may be inferred that the adrenaline has caused vasoconstriction in the test hand. A useful measure of this adrenaline effect is given by $B - E/E \times 100$. It has been shown (Duff, 1952) that the amount of adrenaline required to reduce this expression by 25 per cent may be taken as the threshold of the hand vessels to adrenaline.

Results

Subjects with Normal Blood Pressure. Because of the wide range of response of healthy subjects a large number with normal pressure had to be studied. While the majority exhibited significant vasoconstriction only when the adrenaline levels exceeded 1/16 μg./min., a few reacted with 1/16 or less. A common type of response is portrayed in Fig. 1. The synchronous fluctuation of the blood flow in the two hands (due to bilateral influences unrelated to the infusion) is seen to persist even when adrenaline is being infused into one hand. With the smallest dose of adrenaline (1/64 μg./min.) the greatest individual constriction was 17 per cent and the mean response of the group was under 5 per cent (Table II). With 1/16 μg. adrenaline only 4 of the 20 subjects had significant vasoconstriction, the mean for the group being 11 per cent. With the highest adrenaline level (1/8 μg./min.) 13 of the 23 normal subjects had over 25 per cent vasoconstriction, while 10 had under 25 per cent; the mean for the group was 25 per cent constriction (Table II). Statistical parameters of these observations are given in this Table.

Hypertensive Subjects. When subjects with raised blood pressures were compared under identical conditions with healthy subjects it became apparent that the same stimuli (adrenaline infusions) tended to constrict the hypertensives more. The responses of a woman with a blood

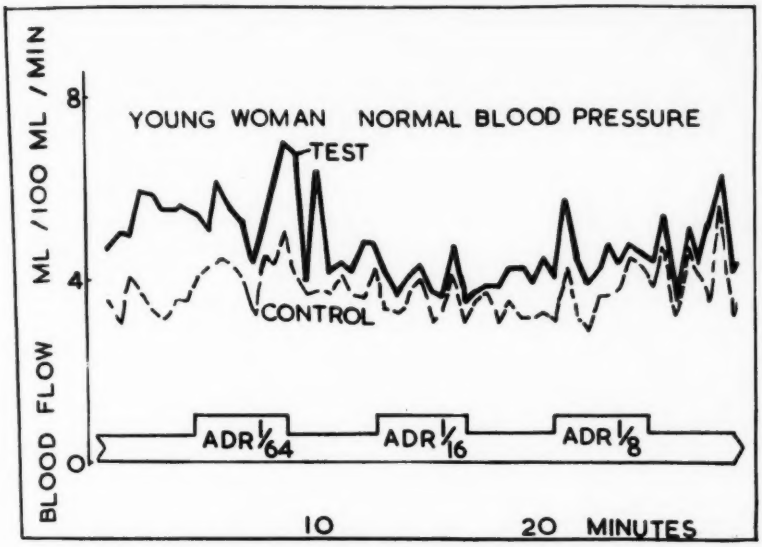

FIG. 1.—Blood flow in the infused test hand (heavy continuous line) and in the control hand (interrupted faint line) of a healthy subject during intrabrachial infusions of adrenaline, 1/64 μg., 1/16 μg., and 1/8 μg./min. None of these infusions caused independent vasoconstriction in the test hand.

TABLE II

MEAN ADRENALINE VASOCONSTRICTION OF GROUPS OF SUBJECTS WITH NORMAL OR WITH RAISED BLOOD PRESSURE

Adrenaline level (μg./min.)		With normal pressure	With raised pressure
1/64	Number of subjects	10·0	10·0
	Mean constriction	4·7	13·8
	Standard error	2·4	6·7
1/16	Number of subjects	20·0	20·0
	Mean constriction	11·3	33·6
	Standard error	3·8	5·0
1/8	Number of subjects	23·0	23·0
	Mean constriction	25·0	52·8
	Standard error	5·6	4·4

pressure of 260/130 are shown in Fig. 2. Clearly all these adrenaline infusions caused independent constriction of the test hand. As in the case of the healthy subjects the range of response of those with hypertension was fairly wide, some of the latter having little or no constriction even with the highest dose of adrenaline. However, there was a particular tendency for those with more severe grades of hypertension to exhibit increased sensitivity to adrenaline. The responses of a woman with malignant hypertension are illustrated in Fig. 3. Even the lowest adrenaline concentration caused 40 per cent vasoconstriction in the test hand. The individual responses at each dose level are summarized in Table II. With 1/64 μg. adrenaline the mean response of 10 hypertensive subjects was

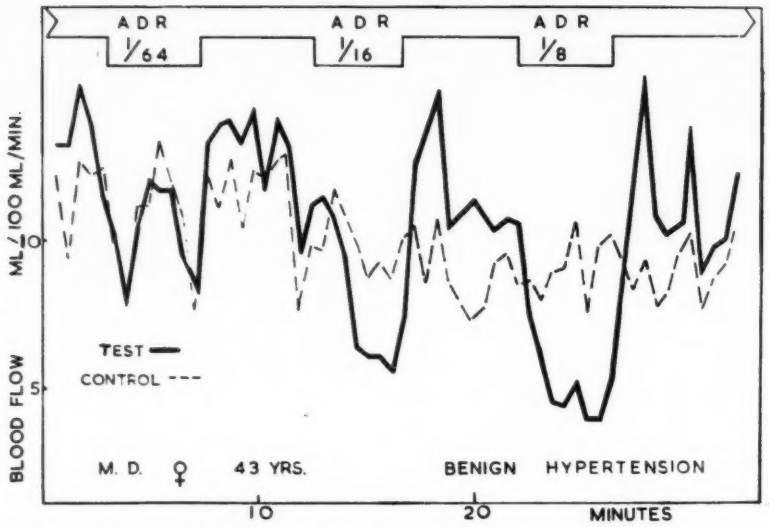

FIG. 2.—Effects of adrenaline infusions on blood flow in the test hand of a subject with hypertension. Significant vasoconstriction resulted from two of the infusions.

13·8 per cent, almost three times that of the normal group. With 1/16 μg. adrenaline 14 of the 20 hypertensive cases had significant constriction, compared with 4 of the normals. As a group the mean response of those with hypertension was about thrice that of the normals. With the highest adrenaline level (1/8 μg.) only 3 of the 23 patients failed to exhibit appreciable vasoconstriction, in contrast with the failure of 10 of the healthy subjects to respond.

The data are summarized in Table II; the differences between the responses of the normal and hypertensive subjects are statistically significant at the 1/16 and 1/8 μg. levels. The mean responses of the two groups of subjects with each adrenaline level are contrasted in Fig. 4.

An expression for the mean vascular sensitivity of a given individual may be obtained by adding the separate responses at each adrenaline level. This is conveniently done by allotting to the various responses a value inversely proportional to the strength of the stimulus as in the following schema.

Percentage vasoconstriction $(B-E/E\times 100)$	Adrenaline concentration 1/64	1/16	1/8 μg./min.	Unit of sensitivity
			under 21	0
			21–40	1
		21–40	41–60	2
	21–40	41–60	61–80	3
	41–60	61–80	81+	4

This scale lays proper emphasis on the threshold response to minimal stimulation. The mean vascular sensitivity of each tested subject was calculated in accordance with the above scale. Those with normal blood pressure ranged from 0 to 3·0, with a mean of 0·7 for the 39 subjects. Those with hypertension ranged from 0 to 3·5, with a mean of 2·0. Thus the mean sensitivity of the hypertensive group was almost three times the normal. The degree of sensitivity was seen (Fig. 5) to be generally related to the severity of the hypertensive process. Some cases of benign hypertension fell within the normal range, but most of those graded progressive were hypersensitive, and the greatest sensitivity was found in those with malignant hypertension.

These experiments have clearly demonstrated a significant difference in vascular sensitivity between two groups of subjects, with normal and raised blood pressures, respectively. Before

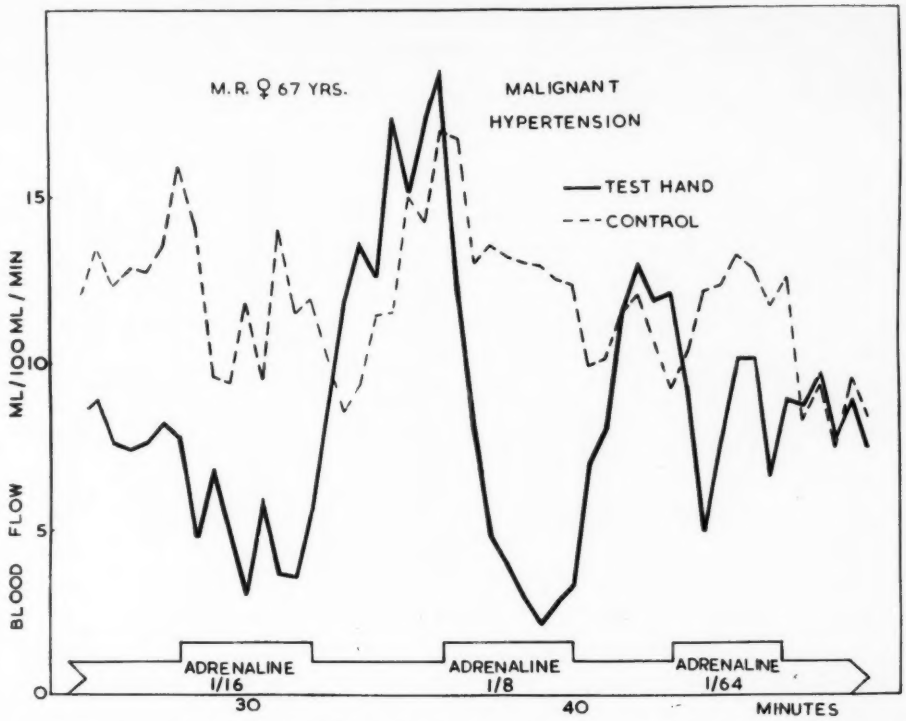

FIG. 3.—Vasoconstriction with adrenaline, even in the low concentration of 1/64 μg./min. in a subject with malignant hypertension.

concluding that the increased sensitivity of the latter is directly related to the hypertension it is necessary to consider critically if the observed difference in sensitivity between the two groups can be attributed to anything other than the hypertension. In addition to blood pressure, the two populations differed in three main respects: age, sex, and profession.

Many of the healthy subjects were younger than those with hypertension, the mean ages of the groups being 29 and 50 years, respectively (Table I). However, about one in four of the former was over 35 and one in three of the latter under 45 years of age. Moreover, the individual responses seemed to be quite unaffected by the age of the subjects, some of the most sensitive being younger than others with less vascular sensitivity. Indeed, the proposition that age has a bearing on vascular sensitivity is clearly not favoured by the haphazard relationship of the two factors.

Most of the healthy subjects were men while most of those with hypertension were women. This might therefore suggest that vascular sensitivity may be greater in women. Examination of individual responses, however, revealed that the vascular sensitivity of eight of the nine normal women was below the normal mean, all but one of those exceeding the mean being men. Moreover, in the hypertensive group four of the seven men, including one with malignant hypertension, had above average sensitivity. There is therefore no support for the hypothesis that sex influences vascular sensitivity.

The remaining factor—occupation—clearly differentiates the two groups, most of the normals being medical students. It could hardly be maintained, however, that medical students are unrepresentative of the general population with respect to such a characteristic as vascular sensitivity to adrenaline.

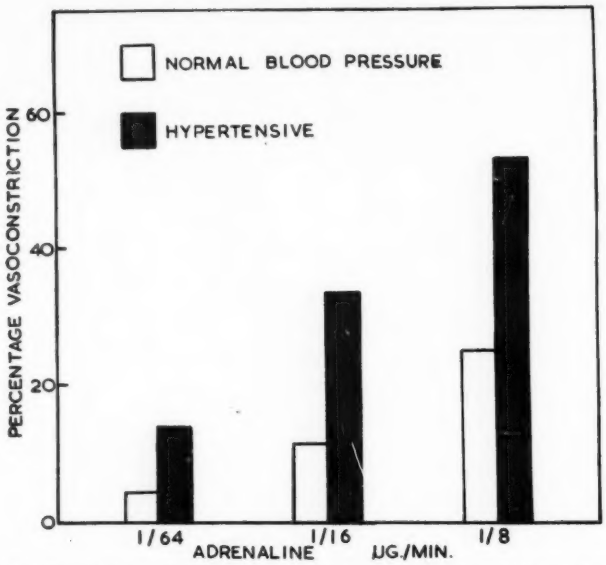

FIG. 4.—Comparison of the constrictor effects of three concentrations of adrenaline in two groups of subjects, with normal and raised blood pressures, showing the greatly increased responses of the latter.

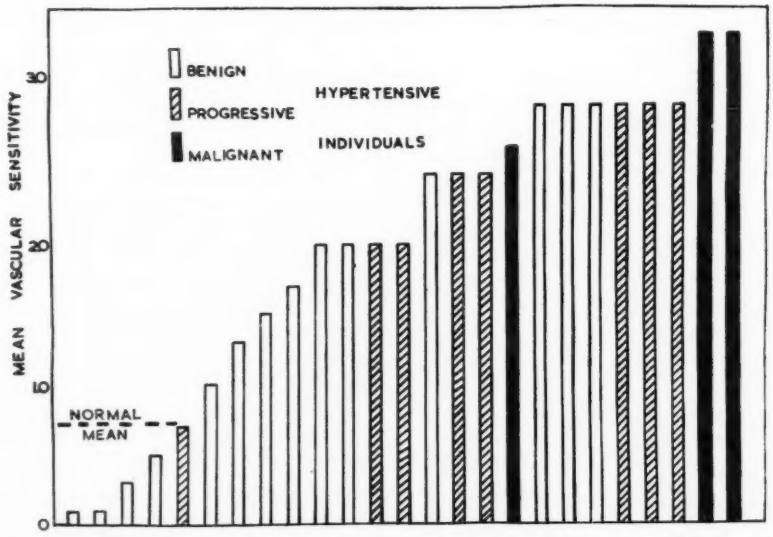

FIG. 5.—Mean vascular sensitivity of subjects with hypertension. All but 5 exceed the normal mean, and in general, those with progressive or malignant hypertension are particularly sensitive to adrenaline.

These considerations do not exclude the possibility that the observed differences in vascular response between the two groups of subjects have a fortuitous relationship to the occurrence of hypertension, though they make it extremely unlikely. The inference that increased vascular sensitivity has something to do with pathological elevation in blood pressure is probably justified.

Discussion

A tendency for adrenaline to cause increased peripheral constriction in hypertension has been demonstrated by these experiments. This is exemplified both by the higher incidence of significant vasoconstriction with small doses of adrenaline in those with hypertension and by their greater response as a group at all adrenaline levels (Table II). Direct evidence has therefore been provided of a general relationship between vascular sensitivity and human hypertension. Reports hitherto published are lacking in comparable quantitative data, but indirect evidence of increased sensitivity to adrenaline in essential hypertension has been described in the nailfold capillaries (Greisman, 1952) and in the bulbar conjunctiva (Lee and Holtze, 1951).

Detailed consideration of individual rather than group responses revealed two important findings. A few of the healthy subjects gave responses far greater than the group as a whole. This may merely express the inherent variability of biological material, but it is equally possible that these more sensitive subjects are indeed pre-hypertensive. Neither speculation conflicts with the concept that hypertension is a " graded characteristic " in the general population (Hamilton *et al.*,1954). It is also noteworthy that a few subjects with benign hypertension had adrenaline responses within the normal range, although most of those with progressive and all with malignant hypertension had increased sensitivity. It may therefore be necessary to recognize two distinct categories of hypertension: (1) clinically mild, without demonstrable abnormality of vascular function; and (2) clinically severe or progressive, with vascular hypersensitivity. It is a common observation that some cases of marked and persistent hypertension may be attended by comparatively little reduction of health and longevity, in striking contrast to the rapid deterioration of others with equal or even lower levels of blood pressure. Until patients have been observed over longer periods it is open to speculation whether the onset of deterioration in hitherto benign cases is related to changes in vascular sensitivity.

The failure to find excessive amounts of adrenaline in essential hypertension has already been noted. The present study provides a basis for the generalized constriction of peripheral arterioles in hypertension in the presence of normal amounts of adrenaline (or other pressor hormones).

Hypersensitivity was not demonstrated in a group of hypertensive cases, all of which were " benign ". In the remainder the abnormality of vascular function tended to be proportional to the severity of the disease when graded according to structural damage. This may suggest that hypersensitivity is the result rather than the cause of prolonged and excessive rise in blood pressure. Increased sensitivity to adrenaline might be due to compensatory hypertrophy of the muscular coat of the terminal arterioles. Alternatively the abnormality of vascular function might be related to those more severe arteriolar lesions responsible for clinically perceptible damage in the retinæ, heart, or kidneys.

The technique of the present study selectively measures the behaviour of the terminal arterioles themselves. It must therefore be emphasized that the findings, being much more specific, bear little relation to tests of generalized cardiovascular function, such as that of Hines and Brown (1936).

The question of vascular sensitivity is of much more than academic interest. The demonstration of a *functional* abnormality of the vessels themselves underlines the purely palliative character of therapy based on chemical or surgical interference with the autonomic nervous system. If subsequent investigation elucidates the nature of the vascular abnormality and its relation to the production and progress of clinical hypertension, this may eventually provide a rational basis for the prevention and treatment of the disease.

Summary

A method of measuring in man the sensitivity of selected peripheral blood vessels has been described. This is based on the quantitative measurement, by venous occlusion plethysmography, of the change in blood flow resulting from the introduction of minimal chemical stimuli into the brachial artery.

In 39 subjects with normal, and 25 with pathologically raised blood pressures, the responses of blood vessels in the hands to adrenaline infusions of 1/64, 1/16, and 1/8 μg./min. have been determined under controlled conditions.

As a group the vascular sensitivity of the hypertensive group has been shown to be almost three times that of the normal group.

In a proportion of subjects with hypertension the vascular sensitivity was found to be normal. In the remainder it was shown to be related to the severity of the hypertensive process.

On the basis of these findings, the recognition of two distinct categories of hypertension has been envisaged; one benign, with normal vascular function, and the other progressive, with vascular hypersensitivity.

I am most grateful to Dr. Geoffrey Bourne and Dr. Graham Hayward both for making patients available and for valuable advice and encouragement; and to Professor Sir James Paterson Ross and Professor Henry Barcroft for providing apparatus and laboratory facilities at St. Bartholomew's and St. Thomas's Hospitals. Some of the data on healthy subjects was obtained in collaboration with Dr. Jean Ginsburg to whom I am indebted for valuable help and criticism. The generous cooperation of patients at St. Bartholomew's Hospital and of medical students at St. Thomas's Hospital made this study possible.

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RADIATION REACTIONS IN THE HEART

BY

A. G. W. WHITFIELD AND P. B. KUNKLER *

From the Departments of Medicine and Radiotherapy, Queen Elizabeth Hospital, University of Birmingham

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There are very few recorded examples of radiation damage to the heart. Davis (1924) using dogs as subjects for experimental radiation found thickening of the walls of their right atria, petechial hæmorrhages, proliferation of connective tissue and cell necrosis with necrotic muscle fibres fused into hyaline masses. The same year Schweizer (1924) reported a case of Hodgkin's disease treated with radiotherapy to the chest. Histological examination of the heart showed atrophy of muscle fibres some of which appeared as dilated empty tubes while the capillaries showed thickened walls and the interstitial tissue vacuolar degeneration. Three years later Hartman *et al.* (1927) published their findings in dogs and sheep exposed to massive experimental radiation of the thorax. The hearts of animals dying within 30 days showed fluid in the pericardial sac, swelling, indistinct striation and irregular staining of the muscle fibres and engorgement of the capillaries; the bundle seemed more resistant than the muscle fibres. Some of the dogs survived for three to five months and in these there was hæmorrhagic infiltration of the right atrium, and thickening of the vessel walls; in the ventricles the muscle fibres showed atrophy, vacuolation and poor striation while in the artium they were largely replaced by areas of homogeneous, pink staining, hyaline degeneration. One of the animals died quite suddenly and unexpectedly. Electrocardiograms (standard leads only) showed T wave inversion often in all three leads, Pardee effects, and in some paroxysmal tachycardia and auricular fibrillation and flutter. These authors also include their findings in the hearts of three patients dying after radiation to the thorax but the abnormalities observed were not very definite and no electrocardiographic studies were carried out. Gloriozor (1949) reported T wave inversion in patients treated with deep X-rays for œsophageal cancer. Liebow *et al.* (1949) in their studies of the victims of the atomic bomb explosions at Hiroshima and Nagasaki found in their hearts hæmorrhages, œdema, focal necrosis and infiltration with plasma and mononuclear cells. Tullis (1949), however, found no significant cardiac abnormalities in swine used as experimental animals at Bikini and elsewhere.

This communication records four cases in which electrocardiographic changes developed during or following radiotherapy to the thorax. In one patient death occurred suddenly and unexpectedly.

Case 1. A man, aged 18, had two years history of painless lymphadenopathy in the left cervical region. Biopsy showed lymphosarcoma. The heart was normal and there were no other physical abnormalities. The X-ray film of the chest was normal. Treated by opposed 44 × 38 cm. cervicothoracic fields, a minimal central axis dose of 2900r being achieved over a period of five weeks (H.V.L. 0·5 mm. Cu., f.s.d. 80 cm., i.f.d. 16 cm.), he developed dyspnœa and dry irritating cough three weeks after conclusion of radiotherapy. Readmitted to hospital two weeks later he was dyspnœic at rest and showed cyanosis on slight exertion. The chest expansion was 3 cm., and there was notable " doorstop " obstruction to full inspiration. X-ray films showed gross bilateral radiation pneumonitis. No abnormal clinical signs were present in the heart and no evidences of cardiac failure. The cardiogram (Fig. 1A) shows flat T waves in leads VR, VL, V5, and V6 and inverted T in leads 1, V2, V3, and V4. Maximum breathing capacity 71 litre/min. All

* Formerly working at the Christie Hospital, Manchester.

divisions of lung volume were reduced. The patient was given A.C.T.H. by slow intravenous drip in a dose of 665 mg. over 26 days with marked improvement in exercise tolerance, chest expansion, X-ray appearances, and tests of respiratory function. There was a slight relapse on cessation of treatment and he was readmitted for further 225 mg. A.C.T.H. by slow intravenous drip over 9 days. At this time no objective cardiovascular abnormality was found and the cardiogram had returned to normal (Fig. 1B). Follow up over three years had not revealed any abnormalities other than residual pulmonary fibrosis.

Case 2. A woman, aged 42, had left radical mastectomy for carcinoma followed by deep

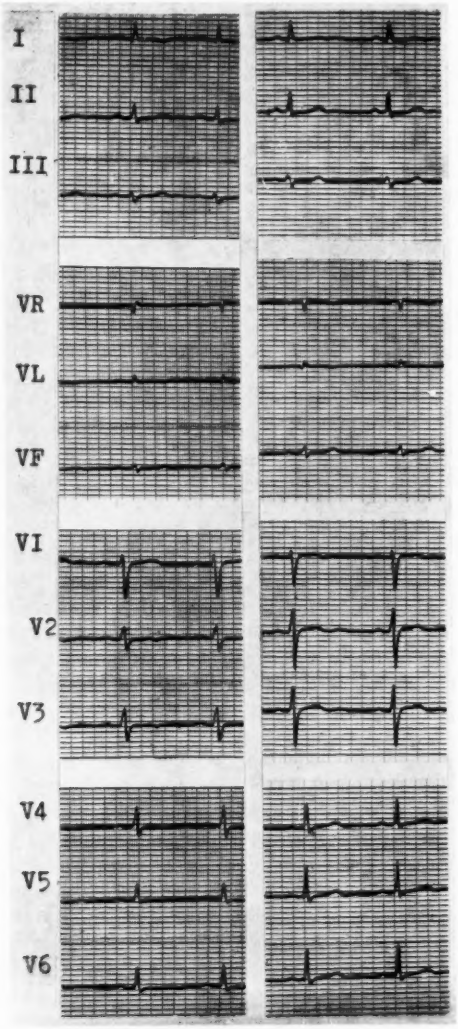

FIG. 1.—Case 1. (A) Inverted T in leads 1, V2, V3, and V4 and flat T in leads VR, VL, V5, and V6 five weeks after the conclusion of cervicothoracic baths.

(B) Physiological electrocardiogram one month later.

X-ray therapy by opposed axillary fields with a single left parasternal field 15×5 cm., the dose given to the latter being 4000r in three weeks (H.V.L. 1·5 mm. Cu., f.s.d. 40 cm.).

Nothing abnormal was found clinically or cardiographically in the cardiovascular system at outset but after one and two weeks radiotherapy there was T wave inversion in leads V1, V2, and V3 (Fig. 2A and B). These abnormalities disappeared during the following two months (Fig. 2C). At no time were there any symptoms or clinical signs in the cardiovascular system.

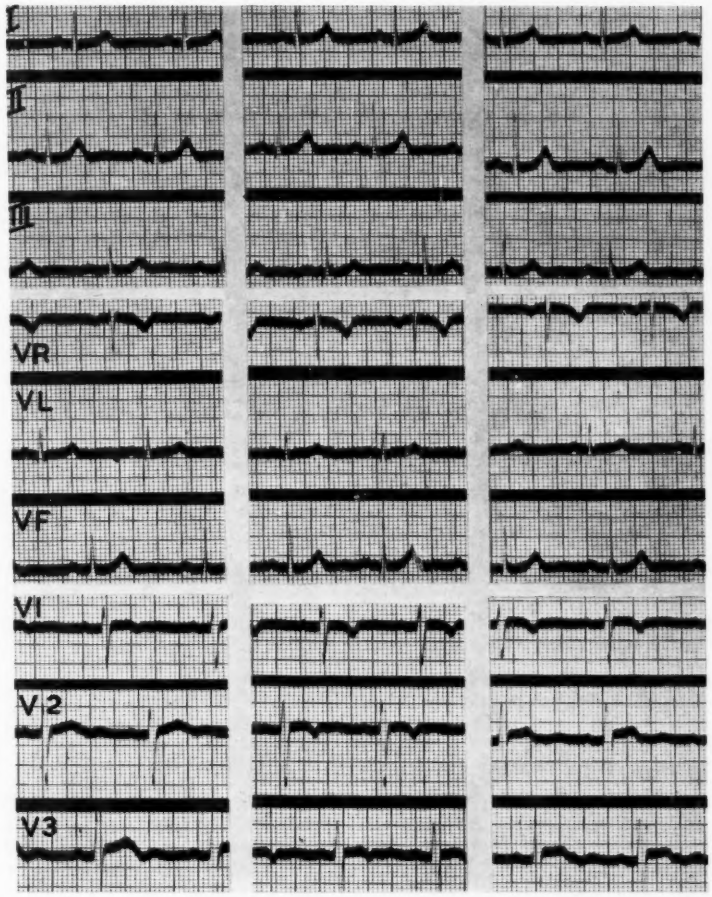

FIG. 2.—Case 2. (A) Normal electrocardiogram before start of radiotherapy. (B) Inverted T in V1, V2, and V3 two weeks after the start of post-mastectomy radiotherapy. (C) Normal electrocardiogram two months after conclusion of radiotherapy. Leads V4, V5, and V6 remained constant throughout.

Case 3. A woman, aged 50, was given post-mastectomy radiotherapy for carcinoma of left breast, by the same technique and to the same dose as described for Case 2.

The cardiovascular system was normal clinically and the cardiogram was normal when X-ray

treatment began (Fig. 3A). After two and a half weeks radiotherapy the cardiogram showed T wave inversion in leads V1 and V2 (Fig. 3B) which had reverted to normal a month later (Fig. 3C). No cardiovascular symptoms or abnormal physical signs were observed at any time.

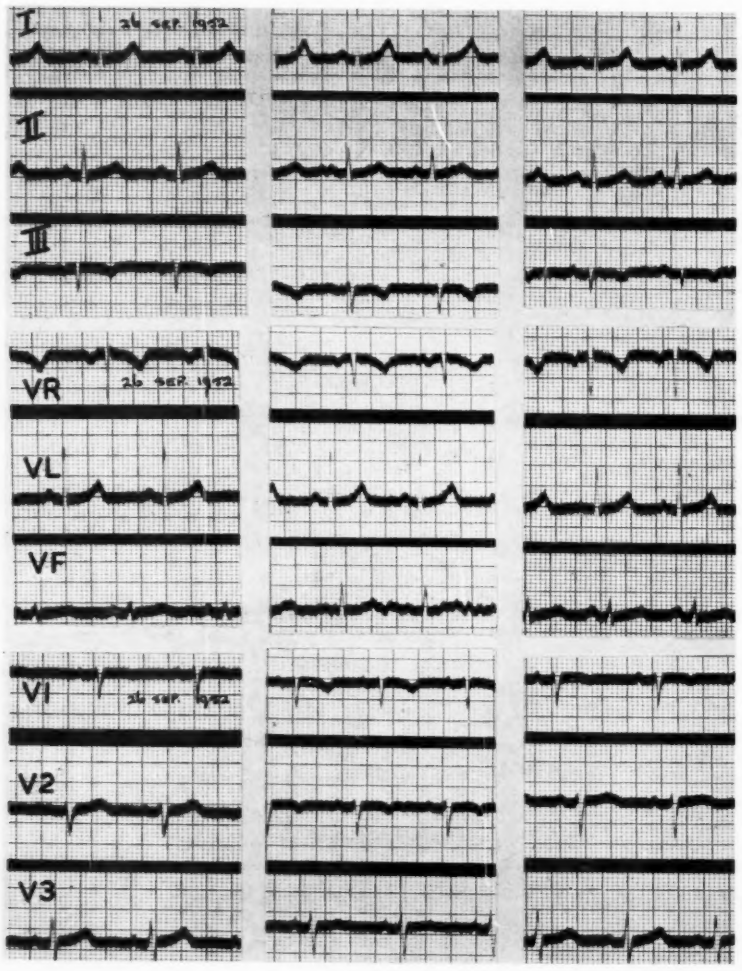

FIG. 3.—Case 3. (A) Normal electrocardiogram before start of radiotherapy. (B) Inverted T in V1 and V2 two and a half weeks after start of post-mastectomy radiotherapy. (C) Normal electrocardiogram one month after conclusion of treatment. Leads V4, V5, and V6 remained constant throughout.

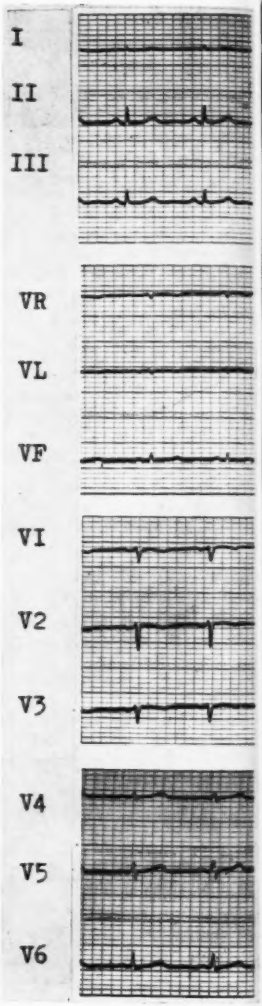

FIG. 4.—Case 4. Inverted T in V1, V2, and V3 five weeks after start of cervicothoracic baths.

Case 4. A man, aged 52, gave a two-months' history of exertional dyspnœa, difficulty in swallowing and weight loss. Examination showed superior vena caval obstruction and enlarged glands in both supraclavicular regions. An X-ray film of the chest showed bilateral paratracheal and

hilar gland enlargement and shadowing in right the mid zone suggesting middle lobe collapse. The œsophagus did not appear to be compressed or invaded but it was displaced to the left at the tracheal bifurcation and to the right lower down. Biopsy of a cervical gland showed carcinoma, the appearances suggesting a bronchial primary. Treated by opposed 40 × 30 cm. cervico-thoracic fields, a minimal central axis dose of 2700r being achieved over a period of six weeks (H.V.L. 0·5 mm. Cu., f.s.d. 100 cm., i.f.d. 18 cm.). Anti-coagulant treatment by dindevan was given throughout the period of treatment in order to minimize risk of lung damage. Radiotherapy produced severe vomiting and prostration and for a time the chest condition worsened, the right lower lobe becoming atelectatic and a pleural effusion developing. Later it was clear that response to treatment was excellent, the difficulty in swallowing and the superior vena caval obstruction disappeared, while the pleural effusion was absorbed, the right lower and middle lobes re-expanding and the glands in the neck and chest becoming much smaller. At the beginning of radiotherapy the cardiovascular system was objectively normal as was the cardiogram. Although no abnormal signs appeared in the heart the cardiogram showed inverted T waves in leads V1, V2, and V3 after five weeks treatment (Fig. 4) and one week later the T waves in all other leads had become flattened. On the following day when it was thought that radiotherapy had given a brief reprieve and arrangements were being made for him to return home, he died suddenly and unexpectedly. Autopsy was unfortunately delayed for three days and considerable autolysis was evident. An anaplastic carcinoma of the right middle lobe bronchus was found with metastases in cervical, paratracheal, hilar, and para-aortic glands. No metastases were found elsewhere. The lungs showed emphysema but no radiation change. The heart and pericardium were normal in the gross and on detailed histological examination except for a very mild degree of coronary atheroma. No cause for sudden death could be found.

Discussion

The electrocardiographic change in each of the four patients here described was remarkably uniform in pattern. Case 2 showed T wave inversion in leads V1, V2, and V3; in Case 3 the T wave change was only seen in leads V1 and V2, but in Case 1 it was evident in all chest leads and also in leads 1, VR, and VL. In Case 4 all leads were abnormal on the day before death. The close temporal relationship between these electrocardiographic changes and X-ray therapy leaves little doubt that they are radiation effects. This contention is supported by their disappearance within weeks of the conclusion of radiotherapy in Cases 1, 2, and 3, the normal electrocardiograms before radiotherapy was begun in Cases 2, 3, and 4, the age of Case 1, and the absence of any subjective or objective evidence of cardiac disease before X-ray treatment was started in all four patients. In Case 1 it might be argued that the changes indicated subacute *cor pulmonale* due to radiation pneumonitis but the record is not that of right ventricular strain and such an explanation is considered unlikely as cardiograms have been normal in all other patients in a personally observed series of 29 cases of radiation pneumonitis some of which were fatal.

The electrocardiographic changes in these four patients show a striking similarity to those described by Hartman *et al.* (1927) in their experimental animals and in these there was unequivocal anatomical and histological evidence of damage to the cardiac muscle, while in those who survived for longer periods there was thickening of the walls of blood vessels and obliteration of their lumen. None of these changes were evident on microscopic examination of the heart in Case 4. The development of electrocardiographic changes during radiotherapy in Cases 2, 3, and 4 and their rapid disappearance after its conclusion in Cases 1, 2, and 3 suggests that they are more likely to result from direct damage to the heart muscle itself than from ischæmia secondary to radiation arterial damage. The finding of Hartman *et al.* (1927) that, in their experimental animals muscle damage occurred early and arterial obliteration late accords with this contention. The changes detected in the electrocardiograms correspond in time with the erythematous skin reactions. In Cases 2 and 3 the dose on the heart was effectively localized to the anterior wall of the right ventricle

and the distribution of the electrocardiographic changes suggests that they may be correlated on an anatomical basis. In Case 1 the whole myocardium was subjected to a dose of 2900r in five weeks and the cardiographic changes correspond well with the homogeneous dose distribution.

Case 4 showed almost exactly the same cardiographic change as Case 1 after a dose throughout the myocardium of 2700r in six weeks though at an earlier stage of the course of radiotherapy T wave abnormality was only apparent in leads V1, V2, and V3.

The sudden and unexpected death in Case 4 remains unexplained but the presence of electrocardiographic changes during life and the absence of any other explanation suggests that it may well have been cardiac.

Although it is probable that in most cases radiation reactions in the heart are, as in Cases 1, 2, and 3, transitory, asymptomatic, and without serious prognostic import, it is probably wise to carry out frequent electrocardiograms whenever X-ray treatment involves subjecting the myocardium to high dose levels. Such practice would in time define the limits of cardiac tolerance to radiation with greater precision and it might also provide a warning that those treating such patients would be prudent to heed.

Summary

Four patients are described in whom electrocardiographic abnormalities developed following radiotherapy to the thorax.

In three of these patients these changes were transitory and asymptomatic; the fourth died suddenly and unexpectedly and no cause for death could be found at necropsy.

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ELECTROCARDIOGRAPHIC CHANGES IN INDUCED HYPOTHERMIA IN MAN

BY

PETER R. FLEMING AND FRANK H. MUIR

From the Cardiac Department, Guy's Hospital

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Numerous papers have been published in the past few years describing the changes in the electrocardiogram of animals submitted to hypothermia (Prec *et al.*, 1949; Bigelow *et al.*, 1950; Osborn, 1953; and Tysinger *et al.*, 1955) and the pattern is now fairly well established. Information regarding changes in the human cardiogram, however, is scanty and has been derived from various sources.

Electrocardiograms of patients suffering from severe exposure to cold have been reported from time to time by Tomaszewski (1938), who was the first to report the "injury potential" at the QRS–ST junction, Wayburn (1947), Graybiel and Dawe (1950), and Laufman (1951). Kossmann (1940) described the cardiograms of nine patients submitted to hypothermia for advanced malignant disease and was the first to describe the progression of the abnormalities with fall in temperature and to comment on the high incidence of atrial fibrillation The results of the horrible experiments at Dachau, in which prisoners were submitted to hypothermia, have been described in detail by Alexander (1949). Finally, two series of cardiograms of patients operated on under hypothermia have been published by Capretti *et al.* (1953) and Hicks *et al.* (1956).

In view of the relatively small number of cases reported so far, less than 50 having been found, we wish to present a series of 29 records of patients submitted to hypothermia for cardiac surgery and to compare them with other published records and with the changes observed in animals.

During the early experimental work on dogs under hypothermia at Guy's Hospital, described by Ross (1954), electrocardiograms were frequently recorded. The changes seen in these records are essentially similar to those described by other workers and will be briefly summarized. It is proposed to refer to experimental work on animals further during the discussion of the human cases, but it should be emphasized at the outset that the changes in the cardiogram during hypothermia in man are not identical with those in animals and conclusions drawn from work on the latter cannot be applied to man uncritically.

In animals, the ventricular rate falls progressively with fall in temperature, and impairment of conduction is manifested early by prolongation of the P–R and QRS intervals; the S–T interval also becomes prolonged (Fig. 1). Nodal rhythm or atrial standstill may occur. At lower temperatures (below 28° C.) ectopic beats and heart block become more frequent and ventricular fibrillation occurs in a proportion of animals, although some workers have succeeded in cooling dogs until asystole occurred at 10°–12° C. (Tysinger *et al.*, 1955). A deformity of the QRS–ST junction occurs in some dogs (Fig. 2) and seems to be a forerunner of ventricular fibrillation but this point will be discussed more fully later.

The present series comprises 29 of the first 30 patients operated on under hypothermia at Guy's Hospital, no records being available in the remaining one. Electrocardiograms were recorded at frequent intervals throughout the operations. A direct-writing Sanborn cardiograph was used with a screened extension to the patient cable; it was found that interference was eliminated by earthing the patient's right leg terminal to the cable itself, the cardiograph also being suitably

grounded. No attempt was made to record during the use of diathermy or the electrical defibrillator, and the electric blanket used during the rewarming period was momentarily switched off when a recording was made. Lead II was recorded almost exclusively and all subsequent remarks apply to this lead unless others are specially mentioned.

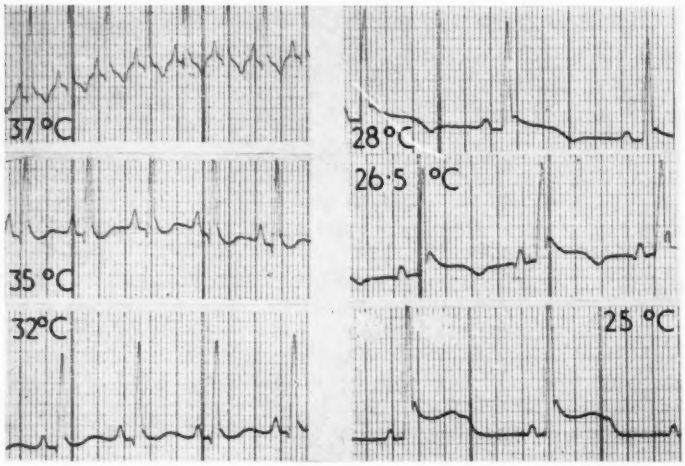

FIG. 1.—Progressive bradycardia with fall in temperature and lengthening of all components of complex. The " injury potential " is first clearly defined at 28° C. and becomes progressively larger. Lead II of dog during cooling.

The methods of cooling used in this series have been fully described by Brock and Ross (1955) and we need only add that the cardiographic changes were the same whatever technique was used. The temperature was always taken in the pharynx.

There were 11 males and 18 females in this series and their ages ranged from 11 months to 47 years. The diagnoses were as follows: atrial septal defect (10 cases), Fallot's tetralogy (6 cases),

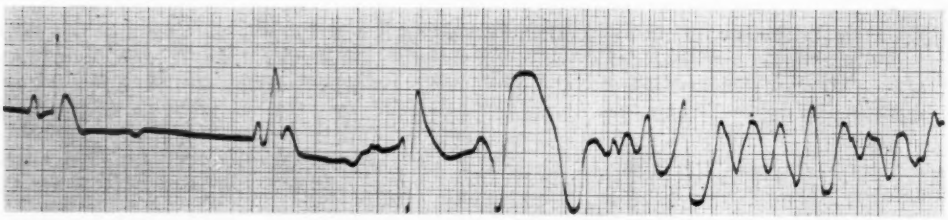

FIG. 2.—The " injury potential " is well developed and the onset of ventricular fibrillation is shown. Lead II of dog at 20° C.

patent ductus arteriosus (5 cases), pulmonary valve stenosis (3 cases), infundibular stenosis (2 cases), ventricular septal defect (1 case), aortic stenosis (1 case), and myxoma of the left atrium (1 case).

As we are only concerned here with the changes in the cardiogram produced by hypothermia *per se*, we have tried to separate off changes due to the anæsthesia or the operation by reference to records of similar operations at normal temperatures (Campbell and Reynolds, 1954) and only

changes that are seen either very infrequently or not at all in such records have been regarded as due to hypothermia.

Changes Found with Hypothermia

Changes in Ventricular Rate. All the patients showed a progressive bradycardia with fall of temperature. In animals the relation between fall of ventricular rate and fall of temperature is linear and this was approximately true for most of our patients, but some showed a steeper fall in rate during the early phase of cooling than later; Hicks *et al.* (1956) noted this frequently. The fall in rate was interrupted by temporary increases when arrhythmias occurred, but with further cooling the ventricular rate continued to fall steadily. The degree of fall in rate varied considerably from patient to patient, the greatest fall being from 185 to 32 and the least from 88 to 72. The means for the whole series were 130 at normal temperatures, falling to 59 at about 28° C. just before circulatory occlusion. We did not often see ventricular rates as low as 30 which Scurr (1955) found frequently, except during circulatory occlusion with which we are not primarily concerned in this study. In animals the bradycardia is not abolished by atropine or vagotomy (Burton and Edholm, 1955) and is therefore presumably a direct effect of cold on the pacemaker.

Changes in Rhythm. Apart from occasional ventricular ectopic beats, the arrhythmias observed most frequently in this series during the early stages of cooling were supraventricular in origin. Ectopic atrial rhythms associated with a wandering pacemaker, including nodal rhythm, were frequently seen. Hicks *et al.* (1956) report similarly, but these arrhythmias are often seen during cardiac surgery at normal temperatures and their association with hypothermia cannot be determined exactly. The general trend of changes is, however, similar to that seen by Crismon (1944) in rats, in which the first effect of cooling was depression of the sinu-atrial node causing bradycardia and the appearance of ectopic atrial rhythms as the excitability of the sinu-atrial node fell below that of other potential pacemakers. Crismon found that complete obliteration of atrial activity occurred before ventricular arrest but Bigelow *et al.* (1950), working with dogs noticed regular atrial contractions by direct inspection at low temperatures (16°–20° C.), while the ventricles were fibrillating.

In man it seems that the depression of activity of the pacemaker with relative increase in excitability of the atrial myocardium proceeds further and atrial fibrillation was seen frequently in this series. Four patients had atrial fibrillation initially; 17 of the remaining 25 developed this arrhythmia at temperatures varying between 35° and 28° C. (mean 31·6° ± 2·4° C.). In our series of cardiograms of dogs atrial fibrillation hardly ever occurred and this agrees with the findings of other workers with animals. There are possible explanations for this discrepancy; the human hearts were all abnormal and so might be expected to develop arrhythmias more readily, and the cooled blood re-enters the circulation in closer proximity to the sinu-atrial node in clinical hypothermia than in our animal experiments. There is, however, a true species difference as normal men accidently immersed in cold water have been found to develop atrial fibrillation frequently (Wayburn, 1947; Graybiel and Dawe, 1950). The high incidence of this arrhythmia is rendered more striking by the fact that it very rarely occurs during cardiac surgery at normal temperatures. Even if the cases of atrial septal defect—in which atrial fibrillation is a recognized complication—are omitted, the incidence is still very high (13 of 19 cases). We did not find any significant difference between the ages of those who did and did not develop atrial fibrillation.

Preliminary study of our earlier cases (Fleming, 1956) suggested that patients who developed atrial fibrillation had a lower immediate mortality than those who remained in sinus rhythm. This unexpected finding has been confirmed by further study and is illustrated in Table I, the difference between the mortality rates of the two groups being statistically significant. Even if the cases of atrial septal defect, which is associated with a better prognosis than some of the other conditions operated on and also with a tendency to atrial fibrillation, are omitted, the difference between the mortality rates remains significant. We are unable to offer any satisfactory explanation of this finding although it is possible to speculate on the role of acetylcholine in this connection,

TABLE I

INCIDENCE OF ATRIAL FIBRILLATION AND ITS RELATION TO PROGNOSIS

	All patients (25)			Omitting those with atrial septal defect (19)		
	Died	Recovered	Mortality rate (percentage)	Died	Recovered	Mortality rate (percentage)
Patients developing atrial fibrillation	5	12	29	4	9	31
Patients remaining in sinus rhythm	6	2	75	5	1	83

and the observations of Riberi *et al.* (1955) on the beneficial effect in hypothermia of producing blockade of the sinu-atrial node with procaine may be relevant.

Ventricular fibrillation occurred in 21 cases in this series. Although the " injury potential ", discussed below, sometimes gave an indication that it was imminent, it appeared more often with little or no warning (Fig. 3). It began during or immediately after circulatory occlusion in several cases and nearly always in association with manipulation of the heart or great vessels. The part played by hypothermia in causing this arrhythmia is therefore difficult to assess and Delorme (1955) has found that it is extremely rare in dogs under hypothermia in the absence of cardiac

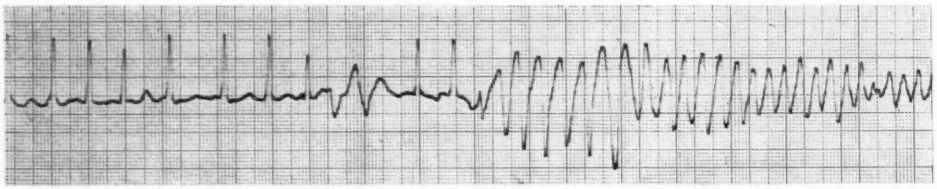

FIG. 3.—Patient with congenital aortic stenosis at 33° C. Atrial fibrillation began at 34° C and the unheralded onset of ventricular fibrillation is shown. At this time, the great veins were being dissected and prepared for occlusion. Lead II.

manipulation. On the other hand, Covino and Charleson (1955) have shown in dogs under hypothermia that the ventricles will respond to artificial stimuli much smaller than would be necessary to excite a response at normal temperatures. They found also that in some dogs the excitability threshold returned to normal levels with further cooling and in these the ultimate outcome was asystole at 15°–18° C.; in the others the threshold continued to decline and nearly all these dogs succumbed to ventricular fibrillation between 19° and 26° C. This clear separation into two groups of animals, one fore-ordained to ventricular fibrillation and the other virtually immune to it, if confirmed, may explain some of the anomalous results reported in connection with this arrhythmia.

Changes in Electrocardiographic Complexes. Previous workers with animals have emphasized consistent lengthening of all the components of the complex and Hicks *et al.* (1956) found the same in their patients.

In this series prolongation of the P–R interval was seen in 21 of the 25 patients initially in sinus rhythm, but it exceeded the upper limit of normal of 0·2 sec. in only 6 of them. The fact that we did not often see great prolongation of the P–R interval is probably due to the frequent occurrence of atrial ectopic rhythms, described previously; and it is possible that, if sinus rhythm had persisted throughout in more cases, more would have shown excessively long P–R intervals. It can be stated, however, that a long P–R interval above 0·2 sec. is not a constant finding during hypothermia as

in one patient who remained in sinus rhythm throughout cooling it increased from 0·15 to 0·2 sec. only, as the temperature fell from 37·5° to 25·5° C. It is well known that bradycardia alone will produce an increase in length of the P–R interval.

Prolongation of the QRS complex occurred more consistently, being recorded in all but two patients, and the upper normal limit of 0·11 sec. was exceeded in 13 of them. The presence of an " injury potential " at the QRS–ST junction, which we have not regarded as part of the QRS complex, renders accurate measurement of the latter difficult and it is worth noting that Campbell and Reynolds (1954) found QRS prolongation occasionally in patients undergoing cardiac surgery at normal temperatures. It seems likely, however, that the consistent finding of prolongation of the QRS in hypothermic animals also applies to man.

Progressive prolongation of the S–T interval (Fig. 4) is the most constant feature of the electrocardiogram during cooling (Muir, 1955). This is to some extent accounted for by the bradycardia

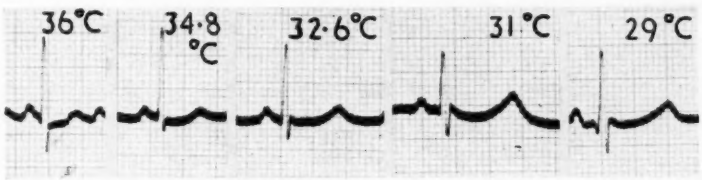

FIG. 4.—Patient with Fallot's tetralogy. The disproportionate prolongation of the S–T interval is shown: P–R increased from 0·12 to 0·16 sec., QRS from 0·06 to 0·08 sec., and QTc from 0·46 to 0·57 sec. Lead II.

but, after making allowance for this by the method of Taran and Szilagyi (1947), an increase in length of from 30 to 70 per cent of the normal can be demonstrated. This apparent delay in repolarization can be compared with the observations on the effect of cooling the anterior chest wall in man by Rahman *et al.* (1954) who interpreted their findings as due to a delay in repolarization of the cooled epicardial surface of the heart.

The changes in the ventricular rate and time-relationships of the components of the electrocardiographic complex are illustrated in Fig. 5 and 6. The most striking feature of the cardiogram during hypothermia is the appearance of the " injury potential " at the QRS–ST junction (Fig. 6 and 7). This was seen in six cases in this series and in all but one of these ventricular fibrillation occurred 30–45 minutes after its first appearance. It was usually best seen in lead II. The nature of this abnormal deflection has been in dispute since it was first observed in a man dying of exposure to cold by Tomaszewski (1938), who believed that it represented gross widening of the QRS. It was also recorded by Kossmann (1940) and Laufman (1951) in human patients but without comment on its ætiology. Osborn (1953) demonstrated by recording leads V1 and V6 in dogs that it did not represent a conduction defect and regarded it as an injury potential in the first part of the S–T segment. He noticed that it was a forerunner of ventricular fibrillation and found that it could be made to decline or disappear by decreasing the concentration of carbon dioxide in the inspired air or by increasing the respiratory minute volume. Siems *et al.* (1955) recorded this wave in 9 out of 20 dogs under hypothermia: they did not comment on its relationship to ventricular fibrillation and believed that it was a prominent Ta wave (atrial T wave). We do not think this likely as we have frequently recorded it during atrial fibrillation (Fig. 6).

Fresh light on the significance, if not the mechanism, of this abnormality has been provided by the researches of Covino and Hegnauer (1955). The work demonstrating increased excitability of the ventricles in diastole during hypothermia has been amplified by the demonstration of a short period of greatly increased excitability (about 80-fold) occurring in some dogs at the QRS–ST junction. When this large rise in excitability was recorded, the " injury potential " always appeared exactly synchronous with it. They also showed that, both at normal temperatures and during

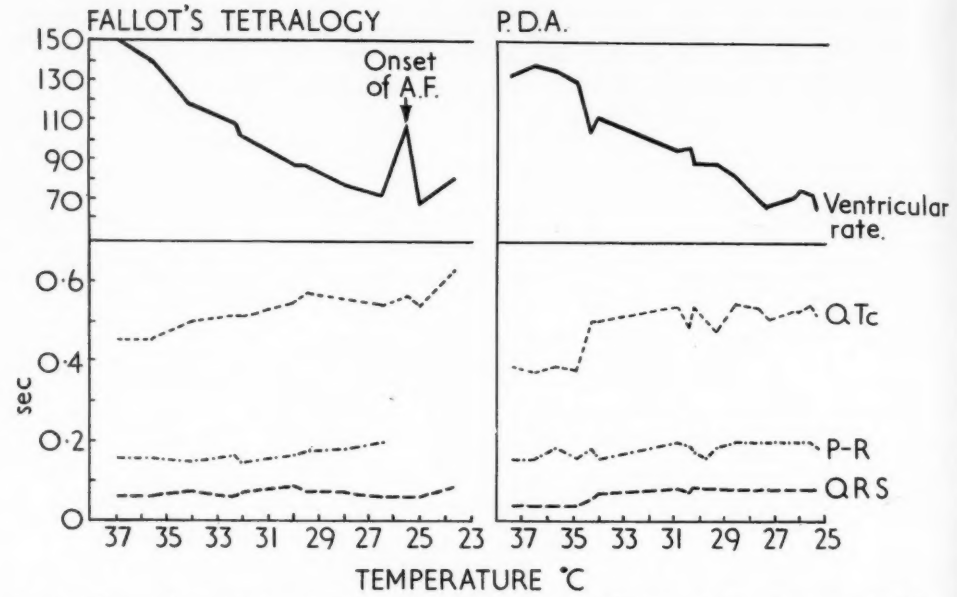

FIG. 5.—Changes in ventricular rate and length of QTc, P–R, and QRS intervals in two patients with fall in temperature.

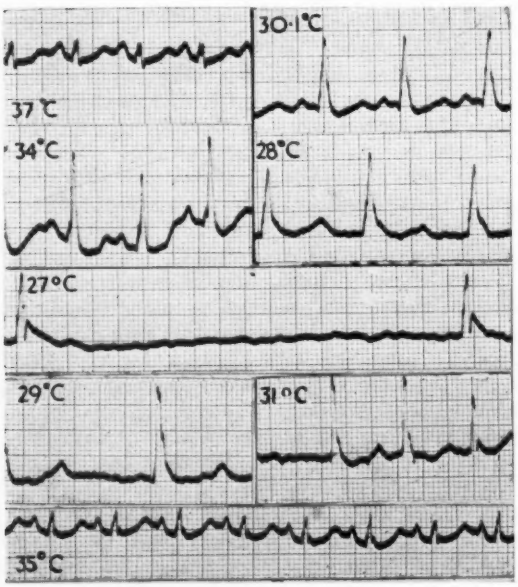

FIG. 6.—Patient with atrial septal defect during cooling and rewarming over a period of 3 hours. All the characteristic features are shown. Atrial fibrillation began at 29° C. without increase in ventricular rate and sinus rhythm returned at 34° C. The "injury potential" was first seen at 27·5° C.; this was the only case in which it was not followed by ventricular fibrillation. Lead II.

hypothermia, this wave was associated with acidosis and that it could be made to disappear by raising the *p*H at normal temperatures but not during hypothermia. The empirical observation that the injury potential is a forerunner of ventricular fibrillation is thus supported by the finding that it is an indication of extreme excitability of the ventricular myocardium.

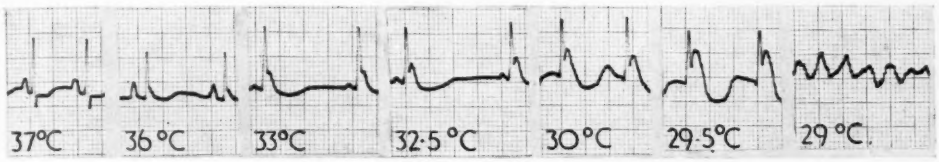

FIG. 7.—Patient with left atrial myxoma. The " injury potential " is first seen at 36° C. and gradually becomes more marked until the onset of ventricular fibrillation 50 minutes later, during the final preparations for circulatory occlusion. Lead II.

Depression of the whole of the S–T segment with or without inversion of the T wave occurred frequently but the changes were inconsistent and bore no relation to the temperature level.

DISCUSSION

We do not propose to discuss the basic mechanisms of the abnormalities recorded further than we have done already. Electrolyte changes have been recorded in animal experiments but the evidence is conflicting and its applicability to man dubious. It seems established that acidosis plays a part in the production of some of the changes in the cardiogram during hypothermia but further than this it is not possible to say. Acetylcholine production is said to be depressed and, if so, this too may play a part. The problems are complex and we have no new evidence to offer.

We have studied the relation of the various features recorded above to the prognosis and, apart from the good prognostic significance of atrial fibrillation, already discussed, have been unable to demonstrate any correlation. Berne (1954) showed that myocardial function in hypothermia was only seriously impaired if the heart rate did not fall, but although his evidence is convincing, we could not establish any correlation between the degree of bradycardia and a good prognosis in our series. The two patients whose ventricular rates did not fall below 100 both did well and the means of the slowest rates recorded were the same for those patients who survived the procedure and those who did not. Similarly the degree of prolongation of the P–R, QRS, or S–T intervals bore no relation to prognosis. Bigelow *et al.* (1950) found in dogs that early inversion of the T wave indicated a poor prognosis but the changes were so inconstant in our cases that no correlation could be made.

The practical value of electrocardiograms in the management of individual patients undergoing hypothermia is not great, but until the metabolic and other changes occurring are better understood, it is clearly valuable to continue to record them for correlation with the clinical condition and prognosis. Findings such as the favourable significance of atrial fibrillation, obtained by this means, are interesting and may prove of some importance.

SUMMARY

A series of electrocardiograms of patients undergoing hypothermia for cardiac surgery at Guy's Hospital has been analysed. The consistent features were a progressive bradycardia associated with evidence of delayed conduction and repolarization as manifested by prolongation of the P–R, QRS, and S–T intervals. Atrial fibrillation occurred frequently and seemed to indicate a favourable outcome. Ventricular fibrillation also was recorded frequently. The " injury potential "

at the QRS–ST junction was recorded in several patients and its association with ventricular fibrillation confirmed.

The mechanisms of these changes are briefly discussed.

We wish to thank Sir Russell Brock for permission to publish these cases and for his co-operation in enabling us to make the recordings.

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EXTRA-CORPOREAL CIRCULATION AND HEART SURGERY

BY

CH. DUBOST, R. HEIM DE BALSAC, R. DE WALL, C. LENFANT, J. GUERY, J. PASSELECQ, M. WEISS, AND J. ROUANET

From the Surgical Centre Marie-Lannelongue (Dr. Sauvage), Cardiological Department (Professor Dubost), the National Centre of Blood Transfusion (Drs. J. P. Soulie and Cagnard), with the help of the Social Security and of the National Institute of Hygiene (Professor L. Bugnard)

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During the last 18 months, we have been investigating the various methods of open heart surgery at the Marie-Lannelongue Surgical Centre. Trials of hypothermia proved unsatisfactory, so we resorted to methods involving an extra-corporeal circulation, employing the simpler systems that use a relatively small flow. In most methods of perfusion during exclusion of the heart and lungs from the circulation, the guiding principle is determination of the minimum blood flow for body weight necessary to maintain life, and this is based on the azygos factor of Andreasen and Watson (1952). We have experimented with the crossed-circulation method of Lillehei and his fellow workers, with the biological oxygenator of Campbell, and with different methods of arterial blood transfusion either alone or combined with hypothermia. In the course of these trials, Lillehei and Dewall perfected their new oxygenator, the advantages of which appealed to us at once so that we adopted it in preference to other systems.

The Lillehei-Dewall Pump-oxygenator System

The system consists of a venous circuit that directs blood from the vena cava to the oxygenator, an arterial circuit that directs oxygenated blood to the aorta, and a finger-type pump that propels the blood in both circuits. Details of the apparatus were shown in the film.

The venous blood is rapidly oxygenated by intense bubbling with oxygen, and the bubbles are then broken up by passage through a tube coated with silicone, and allowed to escape. The oxygenated blood, completely freed from bubbles, accumulates in a reservoir kept warm by a water-bath at 37° C. The arterial circuit starts from this reservoir and includes a filter that permits a rapid flow.

The oxygenator tubes, the reservoir, and the venous and arterial circuits are made of transparent plastic, simply fitted together, the only mechanical device in the system being the pump. We have followed closely the technique devised by Lillehei and Dewall, and we are indebted to Dr. Dewall for his help during a personal visit to our laboratory.

We have introduced certain modifications of the original apparatus which seem to be of value. (1) By employing twin oxygenators, the capacity of the system has been increased from 600–800 ml. at the start successively to 1000–1800 ml. per minute, so that the method is now applicable to adults as well as children. (2) In order to reduce blood loss from hæmorrhage and to diminish the need for multiple transfusions from different donors, we have added another circuit by which blood in the heart cavities, or returning to them during operation, is collected by an aspirator and returned to the oxygenator.

Experimental Results

The pump-oxygenator has been used in 80 dogs. After clamping the venæ cavæ, we have performed cardiotomies involving either the right atrium or the right ventricle, and sometimes both simultaneously. The heart was kept open for 13–40 minutes, and the survival rate was about 80 per cent. All deaths resulted from surgical causes and not from defective operation of the apparatus.

We started with small dogs (up to 20 kg.) using relatively small perfusions of up to 700 ml. per minute, and later we used larger dogs (20–40 kg.) increasing the perfusion above the minimum up to 44–58 ml. per kg. per minute, so that perfusions of 1800 ml. per minute were attained. These good results (80–91% survivals) permitted us to apply the procedure to human surgery.

Clinical Results

Open heart surgery involves much organization and a large team of workers, so that so far we have operated only on five patients, details about whom are given in Table I.

TABLE I
Operated Patients

Case number	Age	Weight (kg.)	Clinical diagnosis and operation findings	Surgical corrections	E.C.C. duration (minutes)	Flow in ml./mn.	Results
1	7	19·6	ASD and large ostium primum	Closure	16	580	Death 24th hour (hæmolysis and anuria) ostium commune and tricuspid and mitral anomalies.
2	4	13·8	Large VSD.	Closure	21	600	Recovery
3	10	20·0	Large VSD and other right-to-left shunt. At operation, large ductus	Division	15	700	Recovery
4	17 mo.	5·9	Pulmonary stenosis and ASD. At operation, infundibular stenosis and ASD (pencil-sized)	None	20	300	Death end of operation (cardiac arrest), regular thickening of pulm. infund., very small ASD, corda, pap. muscle, myocard. and valve anomalies.
5	5	16·0	Large VSD	Closure	20	650	Death 36th hour (heart failure and cardiac arrest). VSD re-opened (stitches cut through). ASD small

Our experience illustrates the difficulty and importance of accurate diagnosis before operation in cases of complex congenital heart disease. For example, in Case 1, the clinical diagnosis was a large atrial septal defect, but operation revealed, in addition, a persistent common atrio-ventricular canal with malformed mitral and tricuspid valves. In Case 3, the clinical diagnosis was ventricular septal defect with pulmonary hypertension, but at operation the ventricular septum proved to be intact and a large patent ductus was found. In Case 4, the clinical diagnosis was atrial septal defect with infundibular pulmonary stenosis, but at operation the pulmonary tract seemed quite patent: at necropsy, the wall of the infundibulum was diffusely thickened and fibrous, and the condition did not appear to be amenable to surgical correction. Ventricular septal defects were closed in two cases, but in both some of the sutures cut out so that complete closure was not obtained, and it seemed likely that this will often happen when the defect is large.

Since this paper was read, we have operated successfully on a sixth case, a girl aged 10, with pulmonary valvular stenosis and retarded physical development. The pulmonary artery was

opened and the three fused commissures were divided with scissors. After operation, the systolic murmur was modified and a pulmonary diastolic murmur was heard, but this disappeared two months later.

Conclusions

Bad-risk cases were purposely chosen for our first surgical trials: as yet our experience is insufficient to be decisive, but both experimental and clinical trials suggest the following conclusions.

The pump-oxygenator-system provides a valuable method of open heart surgery. Our failures arose from surgical or transfusion difficulties and not from any defect of the pump-oxygenator. Now that an extra-corporeal circulation is applicable to adults, we envisage an extension of open heart surgery to acquired heart disease.

Intracardiac surgery encounters two great difficulties: first that of accurate diagnosis before operation and, secondly, the occurrence of multiple lesions that may be beyond the scope of surgical correction. At present, open heart surgery is in its infancy, but new techniques may well improve its results and widen its scope. If the risks are still high, the stakes are great, and the future is promising.

We are greatly indebted to our technical staff, especially R. Rouilloud and L. Aime, for their valuable help both in our experimental and clinical work.

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CLINICAL, PHYSIOLOGICAL, AND PATHOLOGICAL CONSIDERATIONS IN PATIENTS WITH IDIOPATHIC PULMONARY HYPERTENSION

BY

JOHN T. SHEPHERD,* JESSE E. EDWARDS, HOWARD B. BURCHELL, H. J. C. SWAN, AND EARL H. WOOD

From the Sections of Physiology, Pathology, and Medicine, Mayo Clinic and Mayo Foundation,† Rochester, Minnesota, U.S.A.

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Cases of idiopathic pulmonary hypertension are uncommon. Paul Wood (1950) found 6 examples among 233 unselected patients suspected of having congenital heart disease, 152 of whom were catheterized. Dresdale *et al.* (1951) encountered four cases and mentioned that ten cases of pulmonary hypertension without demonstrable cause in which cardiac catheterization had been performed had been reported.

To place patients into this group on the basis of clinical and physiological studies requires that all the conditions of which pulmonary hypertension is but one feature be excluded. There must be, for example, evidence of a normal mitral valve, of a competent left ventricle, and of absence of an abnormal communication between the lesser and greater circulations; and primary disease of the pulmonary parenchyma of the types that narrow the pulmonary vascular bed must have been eliminated. However, even after the most careful clinical and physiological studies, unsuspected malformations of which pulmonary hypertension is a functional accompaniment may at times be demonstrated at necropsy in a case that has been designated as an example of idiopathic pulmonary hypertension.

This communication presents the clinical and physiological findings in ten patients with pulmonary hypertension. In these ten none of the disease states known to be associated with raised pulmonary arterial pressure was demonstrated clinically or physiologically. In four a veno-arterial (right-to-left) shunt was present at the atrial level. Necropsy was done in three of them, in two of which there had been veno-arterial shunts. One of these (Case 8) in which an atrial septal defect of moderate size was present, should be excluded from this paper on the basis of the definition of the syndrome of idiopathic pulmonary hypertension, but careful consideration of the clinical and physiological data, even after the true nature of the condition was known, revealed no feature that would distinguish it from the others reported: hence for reasons of discussion the data for this case have been fully reported.

Special Investigations

Cardiac catheterization was carried out on each patient, using techniques previously described (E. H. Wood, 1950 and 1953). Intravascular pressures were measured by strain-gauge manometer systems (Wood and Sutterer, 1955). The oxygen saturation of blood samples from the heart and great vessels was determined by manometric (Van Slyke and Neill, 1924) and photometric techniques (Wood, 1950).

The objectives at cardiac catheterization are to exclude the presence of any arterio-venous shunt, to exclude a veno-arterial shunt from the right ventricle or pulmonary artery, to obtain the pulmonary arterial and pulmonary arterial " wedge " pressures (Connolly *et al.*, 1954) and to determine the pulmonary and

* Present address: Department of Physiology, The Queen's University, Belfast, Northern Ireland.
† The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

systemic flows and resistances. We believe that in many instances it may be difficult or impossible to decide on the presence or absence of intracardiac or great vessel shunts solely on the basis of the oxygen saturation values of the blood determined by manometric methods. Hence the particular applications of techniques in current use in our laboratory are outlined briefly below.

Oximetry. The absolute reading cuvette oximeter (Wood, 1950), an instrument of high relative accuracy, permitted an immediate reading to be obtained of the oxygen saturation of the blood in the heart and great vessels. Determinations of the oxygen saturation could be made in rapid succession from various sites and, if the significance of any change in saturation was in question, the series of determinations could be repeated as often as required. Such instrumentation greatly facilitates the identification of small arterio-venous shunts by the demonstration of an abnormal difference in oxygen saturation of blood samples withdrawn from the cavæ, right atrium, right ventricle, or pulmonary artery.

Indicator-dilution Techniques. Dye-dilution curves were also used to exclude the presence of any abnormal communication in the heart or great vessels (Nicholson *et al.*, 1951; Broadbent and Wood, 1954) and to localize such a defect if it existed (Swan and Wood, 1953; Swan *et al.*, 1954). This method is especially valuable for the identification and localization of veno-arterial shunts that cannot be localized and, if small, cannot be identified from the oxygen saturation of the arterial blood. The dye-dilution curves were recorded by means of a cuvette oximeter through which blood from the radial artery was permitted to flow, and simultaneously by means of oximeters attached to the pinna of each ear. In some of the earlier cases injections of dye into a peripheral vein only were carried out, while in the cases studied more recently dye injections were made into the chambers of the heart and great vessels through the cardiac catheter (Swan and Wood, 1953).

Inhalation of Gas Mixtures of Different Oxygen Content. The magnitude of an arterio-venous shunt can often be increased if the patient is given 100 per cent oxygen to breathe, and the magnitude of a veno-arterial shunt can often be increased when low-oxygen mixtures are administered (Burchell *et al.*, 1953).

Radial and Femoral Arterial Blood Samples. The presence of a patent ductus arteriosus with reversal of flow through the ductus can be recognized if the oxygen content of the femoral arterial blood is found to be significantly lower than that of blood withdrawn at the same time from an artery in the right arm (Hultgren *et al.*, 1953; Burchell *et al.*, 1953). If the difference in saturation is of doubtful significance, it can be accentuated if the patient breathes low-oxygen mixtures. Indicator-dilution curves recorded simultaneously at each of these sites will differ from one another if a veno-arterial shunt through a patent ductus arteriosus is present (Burchell *et al.*, 1953).

Simultaneous Recording of Pulmonary and Systemic Arterial Pressures. In patients with equal pressures in the right and left ventricles, a change in the relation of the pulmonary-arterial pressure to the simultaneously recorded systemic arterial pressure produced by exercise or by breathing a different oxygen mixture tends to exclude the presence of a patent ductus or ventricular septal defect as the cause of the pulmonary hypertension.

Pulmonary Arterial " Wedge " Pressure. The pulmonary arterial " wedge " pressure should always be obtained in order that obstruction to the pulmonary-venous flow as a cause of the hypertension can be excluded. It has been our experience, however, in certain patients with severe pulmonary hypertension that the catheter may not be advanced into the wedged position in spite of persistent efforts.

Presentation of Data

Clinical Data. The ages of the 10 patients ranged from 24 to 46 years. Nine were women. All complained primarily of increasing weakness and dyspnœa on exertion. The duration of these symptoms varied from a month to 18 years (Table I). Seven of the patients had had one or more attacks of syncope on exertion. An attack, observed in one patient by her home physician, took place when she was carrying out an exercise test: moderate sinus tachycardia was followed by nodal bradycardia when she lost consciousness; there was no convulsion or incontinence. Five of the patients had thoracic pain on effort, which had the general characteristics of angina pectoris: the pain varied from a feeling of pressure in the thorax to pain starting in the chest and extending down both arms. No patient had orthopnœa, paroxysmal dyspnœa, or hæmoptysis, with the exception of one (Case 10), who had had intermittent hæmoptysis for a period of ten days about six weeks before admission.

The characteristic physical finding in all the patients was an accentuated second sound in the

pulmonary area. Four patients had, in addition, a pulmonary diastolic murmur which may have been due to functional incompetence of the pulmonary valve. At catheterization the pulmonary arterial pulse pressure was not significantly greater in these four than in the others of this series. In one a pulmonary systolic murmur of grade I intensity was present. In another, originally referred for possible mitral valvular disease, there was a systolic murmur of grade I intensity at the apex. When this patient returned five months later she had a left recurrent laryngeal nerve paralysis, the systolic murmur had increased in intensity, and a diastolic third sound with a prominent triple

TABLE I

PRINCIPAL FEATURES IN 10 PATIENTS WITH THE CLINICAL DIAGNOSIS OF IDIOPATHIC PULMONARY HYPERTENSION

Case	Age, years, and sex	Pregnancies or miscarriages	Duration of symptoms	Dyspnœa	Chest pain	Syncope	Right heart failure	Prominence of pulmonary arterial shadow	E.C. right ventricular hypertrophy
1χ	24F	4	1 mo.	+	+	+	0	+	++
2	32F	?	1½ yr.	+	0	+	+	++	++
3	35F	5	8 yr.	++	0	+	0	+	++
4	42F	1	11 yr.	++	0–+	0	+	++	++
5	43F	3	16 yr.	++	+	++	0	++	++
6	46F	—	7 yr.	+	0	++	0	++	++
7*	24F	—	7 yr.	++	0	+	0	++	++
8*χ	27M	—	18 yr.	++	+	++	0	++	++
9*χ	30F	—	1½ yr.	++	++	0	0	+	++
10*	38F	6	5 yr.	++	0	0	+	+	0–+

* Complicated by an atrial veno-arterial shunt.
0=absent. +=mild to moderate. ++=severe. χ=necropsy performed.

rhythm was present. The findings, however, could not be interpreted as indicating mitral stenosis, and at catheterization the pulmonary arterial wedge pressure was normal, a fact which suggested that no obstruction existed at the mitral valve. A normal mitral valve was later demonstrated at necropsy.

The electrocardiogram showed right ventricular hypertrophy in all cases. The P waves in six cases had a peaked configuration and exceeded 0·25 mV in one or more leads. X-ray examination showed a prominent pulmonary arterial segment and evidence for right ventricular hypertrophy (Table I). The peripheral pulmonary fields showed normal or diminished vascular shadows and no evidence of parenchymal disease. In no case did physiological studies of pulmonary function (Fowler and Miller, 1954) reveal a respiratory basis for the dyspnœa on exertion. The results of serological tests for syphilis were negative in every case.

The only patients cyanosed at rest were Cases 2, 8, and 10.

Hæmodynamic Data. The data obtained at catheterization are summarized in Table II. The pulmonary arterial pressure was always greatly increased, averaging 111/59 mm. The radial arterial pressure averaged 130/84 mm. The pulmonary arterial wedge pressure was obtained in six and was within normal limits, and the pressure in the right atrium was raised in six cases. Of the four with a veno-arterial shunt, three had right atrial pressures within the range of normal.

The pulmonary flow was always below the range of normal and averaged 1·6 l./min./M.^{2}. In 12 normal subjects of a similar age group studied in our laboratory, it averaged 3·4 l./min./M.^{2}. In two of the patients who did not have a shunt the value for pulmonary flow was determined during moderate exercise: in one it did not change and in the other it increased only from 1·2 to 2·0 l./min./M.^{2}.

The total pulmonary resistance in all the patients was very hign, averaging 2690 dynes/sec./cm.$^{-5}$. In eight of the patients the change in total pulmonary resistance when pure oxygen was breathed instead of air was determined (Table III). With one exception (Case 8) there was no significant

TABLE II

DATA OBTAINED AT CARDIAC CATHETERIZATION

Case	Age, years	Pressure, mm. of mercury					Pulmonary flow (l./min./M².)	Total pulmonary resistance (dynes sec. cm.⁻⁵)	Oxygen saturation percentage (Van Slyke) breathing air		Physically dissolved oxygen in radial artery blood* (volume per 100 ml.)	Hæmoglobin (g. per 100 ml. blood)
		Radial artery S/D	Pulmonary artery		Pulmonary arterial "wedge" (mean)	Right atrium			Radial artery	Pulmonary artery		
			S/D	Mean								
1	24	109/76	82/47	58	4	15/8	1·2	2270	97	52	1·8	13·3
2	32	130/86	100/50	64	—	20/10	2·2	1600	98	64	1·8	15·6
3	35	155/110	94/51	69	—	26/15	1·0	3680	95	44	1·8	17·6
4	42	135/75	137/62	80	8	15/7	2·3	1830	95	68	1·5	16·0
5	43	146/94	144/72	97	—	23/7	1·5	3230	95	55	1·6	16·0
6	46	150/80	99/35	57	13	10/3	2·2	1080	97	71	1·5	14·2
7†	24	100/76	135/84	96	8	18/6	0·9	6390	84	42	0·2	18·2
8†	27	114/66	133/87	105	5	5/0	1·7	2800	81	62	0·1	20·1
9†	30	114/78	94/52	69	3	5/1	2·0	1500	96	68	2·0	15·3
10†	38	150/100	87/46	56	—	8/5	1·1	2490	80	47	0·2	18·7

* Oxygen content minus oxygen capacity while patients breathed 100 per cent oxygen.
† In these patients an atrial veno-arterial shunt coexisted.

decrease. The polycythæmia which was present in six patients (hæmoglobin values ranging from 16 to 20·1 g. per 100 ml.) may have contributed slightly to the increase in calculated vascular resistance.

Patients Without a Veno-arterial Shunt. There was no evidence in Cases 1–6, either from the oxygen saturation of the blood in the right heart and pulmonary artery, or from arterial dilution curves of T–1824, of any abnormal communication in the heart or great vessels. The blood from the radial artery was 95–98 per cent saturated with oxygen when these patients were breathing air and fully saturated when breathing pure oxygen, with 1·5–1·8 volumes of oxygen per 100 ml. of blood in physical solution. In two of these who were studied during exercise there was no fall in arterial oxygen saturation. The indicator-dilution curves for Case 2, shown in Fig. 1, give evidence of the absence of an intracardiac shunt. In this and the other patients without a shunt (Cases 1, 3–6) the only abnormality of the dye curve was the prolongation of the time components associated with a "reduced" cardiac output. In Case 2 there was clinical evidence of tricuspid insufficiency.

TABLE III

CHANGE IN PULMONARY ARTERIAL PRESSURE, PULMONARY BLOOD FLOW AND TOTAL PULMONARY RESISTANCE WHEN THE PATIENTS BREATHED 100 PER CENT OXYGEN

Case	Mean pulmonary arterial pressure (mm. Hg)		Pulmonary flow (l./min.)		Total pulmonary resistance (dynes sec. cm.⁻⁵)		Percentage change in resistance with oxygen
	Air	Oxygen	Air	Oxygen	Air	Oxygen	
2	64	67	3·2	3·1	1600	1730	+8
3	69	72	1·5	1·2	3680	4800	+30
4	80	77	3·5	3·3	1830	1860	+2
5	97	91	2·4	2·3	3230	3160	−2
6	57	56	4·2	4·7	1080	950	−12
7*	96	96	1·2	1·3	6390	5900	−8
8*	105	97	3·0	3·5	2800	2220	−21
10*	56	56	1·8	2·1	2490	2130	−14

* In these patients an atrial veno-arterial shunt coexisted.

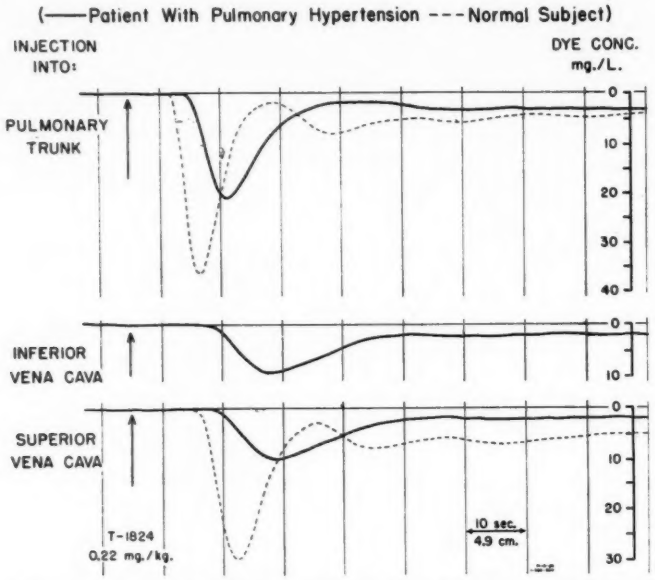

FIG. 1.—(Case 2). Arterial indicator-dilution curves from a patient with idiopathic pulmonary hypertension and a low cardiac output, recorded by means of an oximeter attached to the ear, following injections of T–1824 into (*a*) main pulmonary artery, (*b*) inferior vena cava, and (*c*) superior vena cava, while the patient breathed 100 per cent oxygen. The broken lines, representing dilution curves recorded in a normal subject following injection of an equivalent amount of dye into similar sites, are included for comparison. The dilution curves were also recorded simultaneously in radial arterial blood by means of a cuvette oximeter in every case and were similar in contour to the curves shown. Note the prolongation of all time components and the smaller peak concentration of dye in the curves recorded from the patient. There is no evidence from these curves of an intra-cardiac shunt (compare Fig. 2), but they are consistent with a low cardiac output. The considerable prolongation of the disappearance slopes for the curves following injection into the cavæ, and the more normal contour for the curve recorded following injection into the pulmonary artery are indicative of tricuspid insufficiency.

Patients With a Veno-arterial Shunt. In three of the others (Cases 7, 8, and 10) there was desaturation of arterial blood at rest due to a veno-arterial shunt at atrial level. In Case 8 the arterial oxygen saturation dropped from 86 to 54 per cent with exercise. Case 9, who also had a veno-arterial shunt at atrial level, had a normal arterial saturation at rest, but this decreased to 74 per cent with exercise. The noteworthy findings are described separately for each case.

Case 7. There was no evidence of any arterio-venous shunt from the O_2 saturation of the blood from the right side of the heart. However, the radial arterial blood was only 84 per cent saturated. Calculations on the basis of oxygen-saturation data indicated that about 25 per cent of the systemic flow was derived from a veno-arterial shunt. The direction and magnitude of the shunt were unchanged when this patient breathed pure oxygen instead of air. The dye-dilution curves (Fig. 2) demonstrated a right-to-left shunt of approximately 25 per cent at the atrial level (Swan *et al.*, 1953).

Case 8. This man, aged 27, was cyanosed at rest. When he was 9 years old his parents were first told that he had heart trouble and cyanosis was present: the time of onset of the cyanosis was uncertain. At catheterization repeated determinations of the oxygen saturation of blood in the I.V.C., R.A., and S.V.C. failed to demonstrate the presence of an arterio-venous shunt. The arterial O_2 saturation was only 81 per cent when the patient was breathing air and it was estimated that 40 per cent of the systemic blood came from a veno-arterial shunt. The dye-dilution curves demonstrated a large veno-arterial shunt at the atrial level.

Because of the progressive nature of this patient's symptoms he elected to undergo surgical closure of the defect, which was successfully accomplished. He appeared to be improved, for his cyanosis had disappeared, but about 72 hours after operation he died suddenly. At necropsy he was found to have an atrial septal defect, measuring 2·5 cm. in diameter, and extensive organic pulmonary vascular changes.

The final diagnosis in this case is atrial septal defect with pulmonary hypertension and not idiopathic pulmonary hypertension, as had been suggested by the physiological and clinical findings.

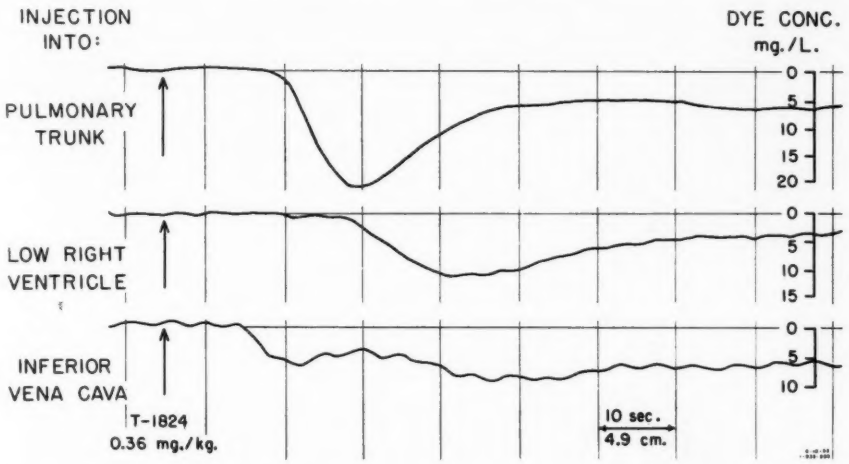

FIG 2.—(Case 7). Arterial indicator-dilution curves recorded by means of an oximeter attached to the ear, following injections of T–1824 into (*a*) main pulmonary artery, (*b*) lower part of right ventricle, and (*c*) inferior vena cava, while the patient breathed 100 per cent oxygen. The curves following dye injections into the pulmonary artery and lower part of the right ventricle are prolonged in their time components but do not indicate any arterio-venous shunt or a veno-arterial shunt at or distal to the lower part of the right ventricle. The curve following injection into the inferior vena cava differs in that the time of first appearance of the dye is shorter and there is an early initial peak of dye concentration. This is due to indicator shunted across an interatrial communication and so reaching the systemic circulation before the remainder of the dye, which has to traverse the pulmonary vascular pathway.

Case 9. The radial arterial blood had a normal complement of oxygen (96% saturated) with the patient at rest and breathing air, and when she was breathing pure oxygen, 2 volumes of oxygen per 100 ml. were present in physical solution. The dye-dilution curves at rest indicated that a veno-arterial shunt existed at the atrial level which amounted to about 6 per cent of the systemic flow. During exercise, however, even when pure oxygen was breathed, the saturation fell to 86 per cent. There was no evidence of any arterio-venous shunt either from the oxygen-saturation values at cardiac catheterization or from the dye-dilution curves. This patient also elected to have a surgical correction of the interatrial communication, but died during the operation. A valve-competent type of patent foramen ovale was demonstrated at necropsy, as the only site for a shunt in the central circulation.

Case 10. The O_2 saturation of the arterial blood was 80 per cent at rest. There was no evidence of an arterio-venous shunt. From the saturation data it was calculated that about 40 per cent and 29 per cent of the systemic flow was composed of shunted blood when the patient breathed air and oxygen respectively. The dye-dilution curves were interpreted to indicate the presence of a moderate right-to-left shunt occurring at atrial level and an insufficiency of the tricuspid valve of significant degree.

PATHOLOGICAL EXAMINATION IN CASES 1, 8, AND 9

Case 1. We are indebted to Drs. L. E. Wold and J. D. LeMar for submitting sections of lung (Fig. 3a). Histological examination of the lungs revealed that, while many of the arterioles and muscular arteries were normal, some, but particularly the arteries, were affected by occlusive lesions. In the arterioles and the small muscular arteries which were affected, the occlusive lesions consisted of fibrous intimal thickening, at

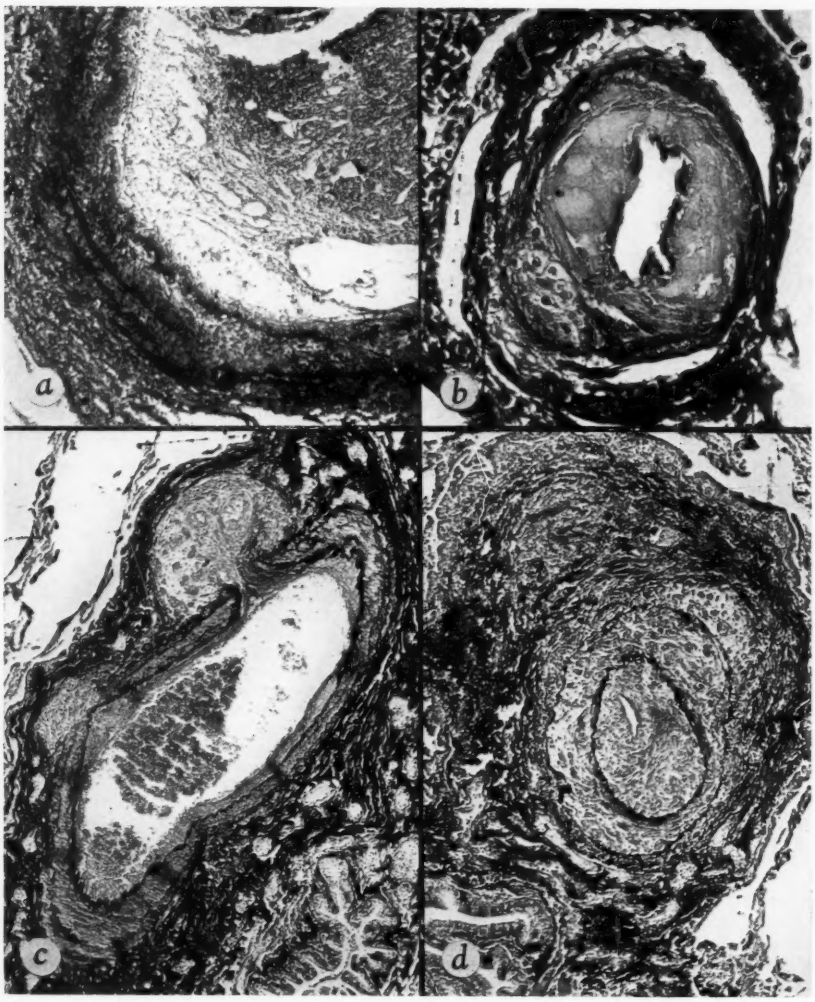

FIG. 3.—Intrapulmonary arteries. (*a*) (Case 1). Elastic artery, showing a thrombus undergoing organization (EL–VG*; ×75). (*b*) (Case 8). Small muscular artery with marked hyaline thickening of the wall associated with luminal narrowing (EL–VG; ×250). (*c*) (Case 8). Large muscular artery, showing healed arteritis characterized by focal scarring of the media and localized intimal thickening. Also a branch of this artery is replaced by vascular connective tissue. This formation is interpreted as representing the end stage of a necrotizing process in the arterial branch (EL–VG; ×45). (*d*) (Case 8). Muscular artery of which the lumen is occluded by vascular connective tissue, interpreted as an organized thrombus. The medial and adventitial layers of the vessel are replaced by vascular connective tissue, interpreted as the healed stage of necrotizing arteritis (EL–VG; ×50).

* EL–VG = Verhoeff's elastic-tissue stain counterstained with Van Gieson's connective tissue stain.

times vascularized. The lumina of many of the large muscular arteries and small elastic arteries were found to be filled with thrombotic material in varying stages of active organization.

Medial hypertrophy of muscular arteries was not a striking feature in this case: in many sites none was present, but in some of the large muscular arteries moderate degrees were evident. The alveolar structure of the lung was normal apart from a solitary focus in which there was pneumonia with abscess formation.

Case 8. The pathological examination of the heart revealed an atrial septal defect, measuring 2·5 cm. in diameter, in the region of the foramen ovale. The heart was enlarged, particularly owing to the thickness of the right ventricle, which on cross-section of the wall measured 1·7 cm., while that of the left ventricle was normal and measured 1·4 cm. The pulmonary trunk was wide, its diameter being 4 cm., while the diameter of the ascending aorta was 2·5 cm.

Microscopically, abnormalities in the intrapulmonary vessels were characterized uniformly by pronounced medial hypertrophy of the muscular arteries, particularly of the larger ones. Although in most of the muscular arteries there was little or no intimal fibrous thickening, there were a few in which the lumen was entirely obliterated by fibrous tissue, at times hyalinized (Fig. 3*b*): this, when present, was more prominent in the small than in the larger muscular arteries. Occasionally, the latter showed formations in which vascular connective tissue replaced all or portions of the arterial wall (Fig. 3*c*). At times this was associated with an organized thrombus within the lumen of a recognizable artery (Fig. 3*d*). The arterioles did not show lesions.

Case 9. At necropsy the heart weighed 550 g. The ductus arteriosus was closed, and there was no ventricular septal defect. In the atrial septum there was a patent foramen ovale 1·5 cm. in diameter guarded by a competent valve which appeared capable of preventing left-to-right flow, but would allow a right-to-left shunt at atrial level. There was striking concentric right ventricular hypertrophy. The gross appearance of the pulmonary tissue was not remarkable.

Histological examination of the lungs revealed that in many of the arterioles there were severe occlusive lesions characterized by cellular, concentric, fibrous, non-vascular, intimal thickening. In serial sections these lesions were shown to be focal, so that on one level the vessel might appear normal and at another completely occluded (Fig. 4a and b).

Uniformly there was pronounced medial hypertrophy of the muscular arteries. Serial sections revealed that frequently the lumen of a small muscular artery was much narrower at its origin than in its more peripheral path: less commonly the diameter was essentially the same at the point of origin as beyond (Fig. 4*c* and *d*).

Thrombotic lesions, either recent and undergoing organization, or healed and represented by plexiform vascular connective tissue, were present in an irregular distribution, involving mainly small muscular arteries. By serial sections it could be demonstrated that at a given level an artery could contain an organizing thrombus but show no evidence of inflammation or destruction in its wall: at another level, however, it would show focal fibrinoid necrosis of the vessel wall with cellular infiltration (Fig. 4*e* and *f*). In one artery this was associated with pronounced arterial and periarterial cellular infiltration associated with fibrous narrowing of the lumen. In this instance the infiltrating cells were mainly neutrophils, but in one focus in a periarterial location, multinucleated giant cells formed part of the cellular infiltrate.

Comment

The characteristic clinical features of idiopathic pulmonary hypertension have been described by Dresdale *et al.* (1951), (1954), P. Wood (1952), and others. Our patients conform to this pattern, and it appears that the syndrome can be explained on the basis of pulmonary hypertension associated with a low and probably fixed cardiac output. Certain features merit more detailed consideration.

Sex Incidence and Pregnancy. With the exception of Case 8, in which an atrial septal defect was found at necropsy, all the patients in this series were female. This introduces the question whether idiopathic pulmonary hypertension may be initiated by non-fatal amniotic embolism. A review of the marital histories of the women revealed that four gave no history of pregnancy. The histological examination of the lungs of the two female cases examined at necropsy (one of whom had been pregnant) showed no features that could be interpreted as residue of amniotic embolism. Though no association with pregnancy can be established, the question remains whether in some way the pulmonary obstructive lesions are related to menstruation, whether the conditions set up by the menstrual cycle can stimulate thrombosis in the pulmonary vessels or in the uterine vessels which in turn leads to small and recurring pulmonary emboli. The arteriolar lesions in Case 9, however uniform, may conceivably be related to previously recurring thrombi or emboli, as postulated for cases of this kind by Barnard (1954). The answer cannot be given at present.

Cyanosis. Peripheral cyanosis may occur even when the arterial oxygen saturation is normal, because high extraction of oxygen consequent to the reduced cardiac output leads to a high degree

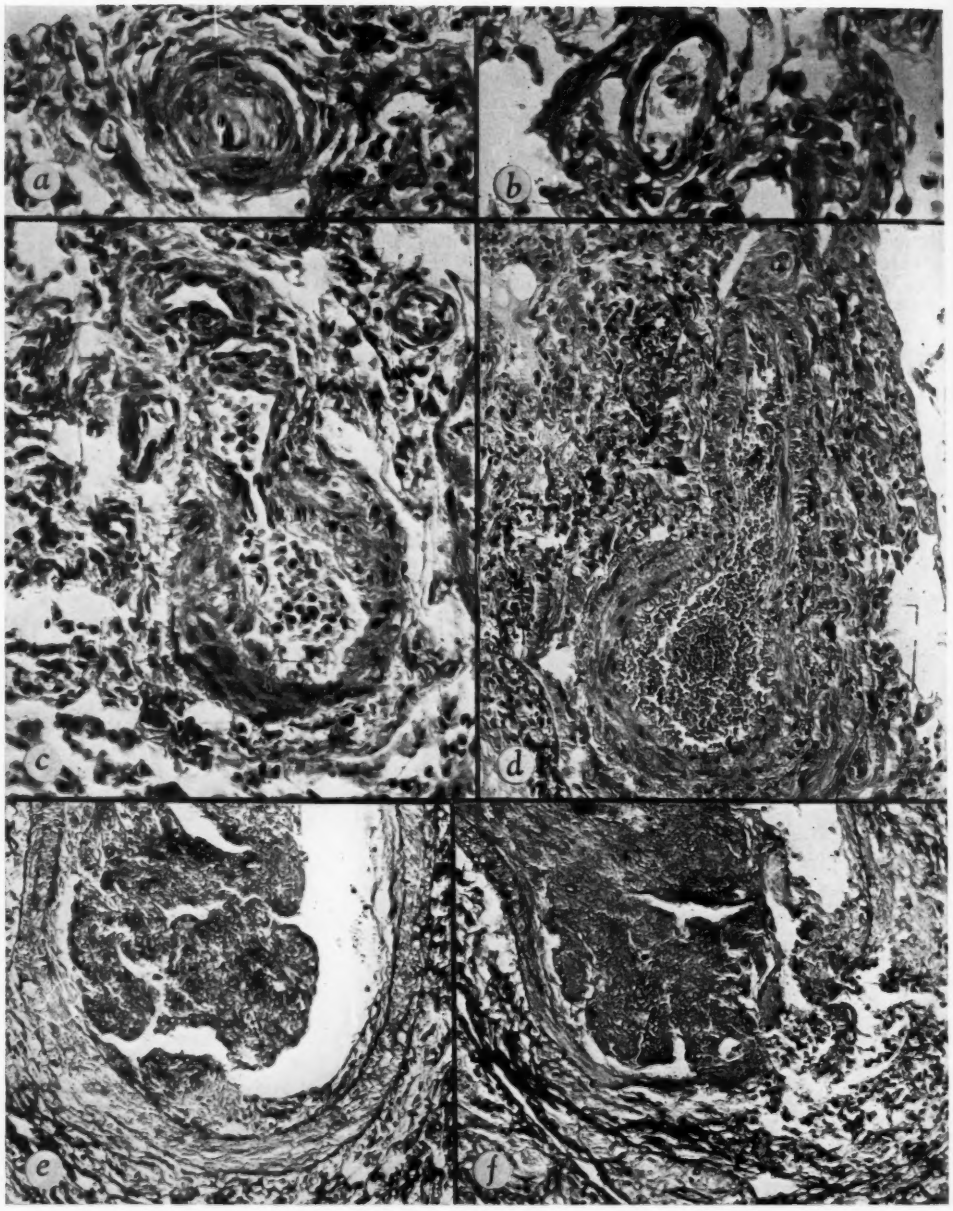

FIG. 4.—(Case 9). Intrapulmonary vessels. (*a*) Arteriole, showing marked concentric, nonvascular intimal thickening causing virtual obliteration of the lumen (hæmatoxylin and eosin; ×310). (*b*) Same arteriole as illustrated in (*a*) but at a different level, showing the wall here to be normal (hæmatoxylin and eosin; ×310). (*c*) Large muscular artery and its branch. There is medial hypertrophy, particularly of the parent vessel, and localized narrowing of the branch at its origin. This narrowing was true, as demonstrated by examination of the serial sections (hæmatoxylin and eosin; ×250). (*d*) Muscular artery and its branch, showing no narrowing at the origin of the branch, in contrast to the picture in (*c*) (hæmatoxylin and eosin; ×135). (*e*) Muscular artery containing a thrombus. At this level no significant alterations in the arterial wall existed (EL–VG; ×150). (*f*) Same artery as illustrated in (*e*) but at a different level, showing the thrombus associated with focal fibrinoid necrosis of the arterial wall (EL–VG; ×150).

of oxygen unsaturation of the venocapillary blood, as in Case 2; it is not due to arterial hypoxæmia. It is noticeable where the local blood flow is small in relation to the oxygen utilization of the tissues. Desaturation of the arterial blood, when present, is not a consequence of the pulmonary hypertension *per se*, but results from a veno-arterial shunt through a valve-competent foramen ovale (Cases 7, 8, and 10).

Syncope. Seven of the 10 patients gave a history of syncopal attacks. Howarth and Lowe (1953) measured the brachial arterial pressure in two patients with primary pulmonary hypertension and two with the tetralogy of Fallot during induced syncope after exertion. The blood pressure fell gradually after exertion. Sinus bradycardia and loss of consciousness occurred only when the systemic pressure reached low levels. In one patient with pulmonary hypertension, as the systemic pressure fell, the pulse pressure in the right ventricle decreased, with a rise in the diastolic or " filling " pressure. These results indicated an acute failure of the right ventricle due to increase in right ventricular pressure with exercise.

Pulmonary Arterial Wedge Pressure. In the six patients in whom these pressures were obtained, they were within normal limits. In spite of repeated attempts in the others, a wedge pressure was not obtained: there was, however, complete absence of any evidence suggesting disease of the mitral valve or left ventricular failure. Occasionally, when apical murmurs are absent, a case of mitral stenosis may be misinterpreted as an example of idiopathic pulmonary hypertension. In the presence of a diastolic murmur due to functional incompetence of the pulmonary valve following idiopathic pulmonary hypertension, mitral stenosis may be suspected clinically, as in Case 1 of this series. The demonstration of a normal wedge pressure minimizes these two errors.

Pulmonary Resistance. In the presence of a normal wedge pressure and a high total pulmonary resistance, the obstruction to flow is situated proximal to the pulmonary capillary bed. This is the case in idiopathic pulmonary hypertension. Although the average total pulmonary resistance was higher in our 10 cases than in most cases of ventricular septal defect, patent ductus arteriosus, or atrial septal defect and pulmonary hypertension, the resistance may be just as high in individual patients suffering from the latter conditions (Swan *et al.*, 1954). Hence the magnitude of the pulmonary arterial resistance is not in itself of differential value in distinguishing between these conditions.

The inhalation of 100 per cent oxygen frequently decreases the total pulmonary vascular resistance in patients with congenital heart disease and pulmonary hypertension. For example, in six patients not part of this study (four with patent ductus arteriosus and two with ventricular septal defects) in whom the total pulmonary vascular resistance while breathing air varied from 480 to 3215 dynes sec. cm.$^{-5}$, the decrease varied from 27 to 64 per cent, with an average decrease of 38 per cent. Of the eight cases in the present series in which the effect of breathing oxygen was studied, four showed no change or a slight increase and four showed some decrease, but in only one was this thought to be significant (Table III). While the mechanism by which the oxygen produces a decrease in resistance is unknown, a failure of the resistance to decrease indicates that the calibre of the vessels in the lung remains unchanged, possibly because of the organic changes.

The Presence and Significance of an Intracardiac Shunt

Special laboratory investigations, including cardiac catheterization, are mandatory if a firm diagnosis of idiopathic pulmonary hypertension is to be made during the life of the patient. The nature of the diagnostic problem differs according to whether or not desaturation of the systemic arterial blood is present. In this regard the variability obtained for normal persons (range of calculated values, 94·5–101 per cent; Wood, 1949) makes it difficult to assess the significance of oxygen saturation values in the lower range of normal. When the arterial saturation exceeds 96 per cent while the patient breathes air, both at rest and during exercise, it is reasonable to assume that there is no impairment of oxygenation in the lungs and that no veno-arterial shunt of significance exists. For patients with systemic arterial saturations which lie in the lower range of normal, additional studies are required to exclude the presence of a veno-arterial shunt.

Patients With Normal Arterial Oxygen Saturation. Of the 10 patients of the present series considered to have idiopathic pulmonary hypertension, six did not have a veno-arterial shunt. One (Case 2) of these

six was cyanotic, but no arterial desaturation was demonstrated: the cyanosis was considered to be due to a high degree of extraction of oxygen from the capillary blood. In these patients without a veno-arterial shunt the investigations were directed toward excluding arterio-venous shunt at the pulmonary, ventricular, or atrial levels.

Patients With Arterial Desaturation. In patients with arterial desaturation or in patients in whom the systemic arterial saturation is within the range of normal at rest although a veno-arterial shunt of small magnitude is present, a diagnosis of idiopathic pulmonary hypertension can be made only if the veno-arterial shunt occurs at the atrial level via a valve-competent foramen ovale. Patent ductus arteriosus, aortico-pulmonary septal defect, and ventricular septal defect complicated by pulmonary hypertension must each be excluded. As mentioned earlier, the use of indicator-dilution techniques makes it possible to solve this problem by establishing the location of a defect through which a veno-arterial shunt is occurring. We have encountered cases of pulmonary hypertension in which studies of the oxygen saturation of the blood gave no significant evidence of any intracardiac shunt, only to find that the technique of selective injection of dye demonstrated the presence of a ventricular septal defect. Hence these cases could be excluded.

The value of the dye-dilution method in localizing the shunt to the artrial level is illustrated by Cases 7, 8, 9, and 10 of the present series (Fig. 2). Of the four patients with a veno-arterial shunt at the atrial level only two were definitely cyanosed at rest, although desaturation of the arterial blood at rest was found in three of these four: the fourth (Case 9) had arterial desaturation only on exercise.

In these patients with interatrial communication, the pulmonary hypertension may be idiopathic associated with the secondary opening of a normal valve-competent foramen ovale, or it may represent a complication or a functional accompaniment of a true anatomical atrial septal defect. The presence of a valve-competent (normal) foramen ovale can be excluded if the oxygen saturation of the blood in the right atrium exceeds that in the venæ cavæ. Further, the arterial dilution curves recorded following injection of T–1824 into right and left pulmonary arteries frequently serve to indicate the presence of an atrial septal defect. However, in the presence of negative findings, this differentiation cannot be made. In Case 8 there was no evidence of an arterio-venous shunt, either by repeated oxygen-saturation determinations or by the dye-dilution method. Necropsy subsequently revealed an atrial-septal defect of typical appearance, which measured 2·5 cm. in diameter: the right ventricular wall showed pronounced concentric hypertrophy, but the chamber was not dilated: these features were different from those in patients with atrial septal defect and left-to-right shunts but no pulmonary hypertension, and suggested that a prominent left-ro-right shunt had never been present. The clinical and physiological findings in this patient were entirely consistent with the diagnosis of idiopathic pulmonary hypertension with a right-to-left shunt through a valve-competent foramen ovale. The finding at necropsy of a true anatomical atrial septal defect makes it necessary to reclassify this case as one of atrial septal defect associated with pulmonary hypertension.

In Case 9 the differentiation from atrial septal defect was made when a valve-competent foramen ovale was found at necropsy. In Cases 7 and 10 no final answer can be given as to whether they are examples of idiopathic pulmonary hypertension with patent foramen ovale on the one hand or of atrial septal defect associated with pulmonary hypertension on the other.

Structural Pulmonary Vascular Changes

The pathological studies made in Cases 1, 8, and 9 do not permit a firm conclusion to be drawn as to the cause of the pulmonary vascular changes. In Case 1 the lesions are consistent with pulmonary embolism or thrombosis, although no recognized cause for either existed. In Case 8 the striking feature was the medial hypertrophy of the muscular arteries, which may represent a persistence of the fœtal characteristics of the pulmonary arteries (Civin and Edwards, 1950). In Case 9 the lesions may have been thrombo-embolic in origin, but this cannot be stated with finality.

One feature was brought out by this study: an arteriole that seems normal may in fact at another level be involved by a lesion that entirely occludes its lumen. This may explain some of the opinions expressed in the past which have indicated that the number of occluded arterioles seemed inadequate to be responsible for the degree of elevation of pulmonary pressure present in given cases.

Another feature brought out by the study of serial sections was that at a certain level an artery might be occluded by a bland thrombus which was not associated with changes in the arterial wall. These features would make it difficult to explain the thrombus as having arisen locally and embolism might be given as a probable cause for the occluding thrombus. With serial sections it was shown that

at other levels the artery occluded by a thrombus might have a necrotizing process in it at which site primary thrombosis occurred: the thrombus seen at another level in the same vessel would then properly be viewed as having been propagated from this primary site.

The presence of necrotizing arterial lesions associated with thrombosis in Case 9 has some bearing on the understanding of lesions in Case 8, where there were foci in arterial walls without the usual elements of the arterial wall. At such sites there was vascular connective tissue. Such lesions, in Case 8, we thought to represent end stages of more acute and necrotizing lesions of the types observed in Case 9. The necrotizing arteritis is considered to be secondary to the presence of the pulmonary hypertension. We have observed this type of lesion both in acute and in healed stages in the lungs of patients with other conditions, all of whom had associated severe pulmonary hypertension, and we believe the arteritis to be a complication of this. The occurrence of such lesions makes one recall that in the systemic circulation necrotizing arteritis may complicate severe hypertension. Thrombotic lesions, both acute and organized, which complicate necrosis of arteries lead to occlusion of vessels. In this way the necrotizing process may be considered to contribute to the pulmonary hypertension. It should not, in our view, be considered an important element in the pathogenesis of pulmonary hypertension, however, since such lesions are comparatively few and they seem to complicate the state in which severe pulmonary hypertension exists rather than to play a role in its inception.

Summary

This report concerns 10 patients in whom a diagnosis of idiopathic pulmonary hypertension was made on the basis of clinical and physiological studies. Such a diagnosis is chiefly a process of elimination of other types of heart disease of which pulmonary hypertension is a functional accompaniment. The certain differentiation can be made from the great majority of such conditions by the critical application of certain physiological techniques, notably the indicator-dilution method. The only intracardiac shunt consistent with a diagnosis of idiopathic pulmonary hypertension is a veno-arterial shunt through a valve-competent patent foramen ovale. By definition, pulmonary hypertension associated with a true atrial septal defect is not of the idiopathic type. However, the certain differentiation by clinical or physiological methods of a veno-arterial shunt occurring via an unsealed valve-competent foramen ovale or via a true atrial septal defect may be impossible, as attested by Case 8 of the present series.

Post-mortem studies were carried out on the three patients who died. In one, the only man in the series, a true atrial septal defect was found, but the appearance of the heart did not suggest that a large left-to-right shunt had ever been present. The histological appearance of the small pulmonary arteries was varied, but examination of serial sections along the course of a vessel often revealed localized obstructions, which were frequently seen in vessels, the lumina of which were unobstructed throughout most of their length. In the patients studied post mortem the organic changes in the pulmonary vessels appeared sufficient to account for the pulmonary hypertension.

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IDIOPATHIC PULMONARY HYPERTENSION

BY

DONALD HEATH,* WILLIAM WHITAKER, AND JAMES W BROWN

From The Regional Cardiovascular Unit The City General Hospital and the University Department of Medicine, The Royal Hospital, Sheffield

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Since it became possible to record pulmonary artery blood pressures directly by cardiac catheterization, several authors have described severe pulmonary arterial hypertension in patients without any apparent predisposing cause such as a septal defect or mitral stenosis. The purpose of the present communication is to describe four further patients with idiopathic pulmonary hypertension and to emphasize that the clinical features and pathological lesions in the lungs of these cases are similar to those occurring in other patients with severe pulmonary hypertension secondary to congenital septal defects. Heath and Whitaker (1956) have pointed out that all patients with severe pulmonary hypertension present a distinct clinico-pathological entity, which they term hypertensive pulmonary vascular disease; it is dominated in life by the symptoms and signs of pulmonary hypertension and characterized at autopsy by specific changes in the small pulmonary blood vessels.

Case Reports

The clinical picture in all four cases was strikingly similar and was dominated in each instance by the classical signs of pulmonary arterial hypertension. These were giant *a* waves in the jugular venous pulse (Fig. 4), a parasternal heave, a systolic lift over the right ventricular outflow tract, and a palpable second sound in the pulmonary area which was loud and split on auscultation. All were in congestive cardiac failure. In each case the electrocardiogram showed right ventricular hypertrophy and peaked P waves suggestive of right auricular hypertrophy (Fig. 1), while the teleradiogram showed overall cardiac enlargement (Fig. 2) which erroneously seemed on fluoroscopy to be due to left ventricular hypertrophy (Fig. 3). In all there was increased prominence of the pulmonary artery and expansile pulsation of its main branches not amounting to a hilar dance (Fig. 2 and 3). In none were the peripheral vessels of the lung clearly seen. In Cases 1 and 4 angiocardiography confirmed the aneurysmal enlargement of the pulmonary arteries and the absence of a congenital cardiac anomaly (Fig. 2). The flow of blood through the lungs in both was sluggish and eight seconds after injection no contrast medium had appeared in the left side of the heart. Cardiac catheterization demonstrated severe pulmonary arterial hypertension (Fig. 4) in Case 1, 2, 3, and 4 and no evidence of an intracardiac shunt. In each case the radial pulse was normal or of poor volume, while the systemic blood pressure was normal or low (Fig. 4).

Similarly, in each of the cases that came to necropsy (Cases 1, 2, and 3) certain histological changes in the pulmonary blood vessels occurred constantly (Fig. 5). The pulmonary arterioles ($<100\mu$ in external diameter), which in normal human lung consist of a single elastic lamina lying between the endothelium and a thin adventitia, showed a distinct muscular media between two elastic laminæ, a thickened adventitia, and severe intimal fibrosis (Fig. 5). The muscular pulmonary arteries (100–1000μ in external diameter) had a thickened adventitia and severe intimal fibrosis but in

* Leverhulme Research Scholar, Royal College of Physicians

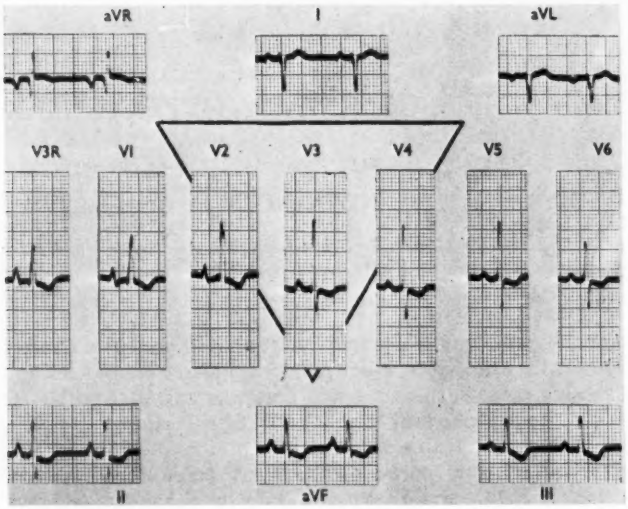

FIG. 1.—Electrocardiogram, showing right axis deviation, right ventricular hypertrophy, and clockwise rotation of a vertical heart. Case 4.

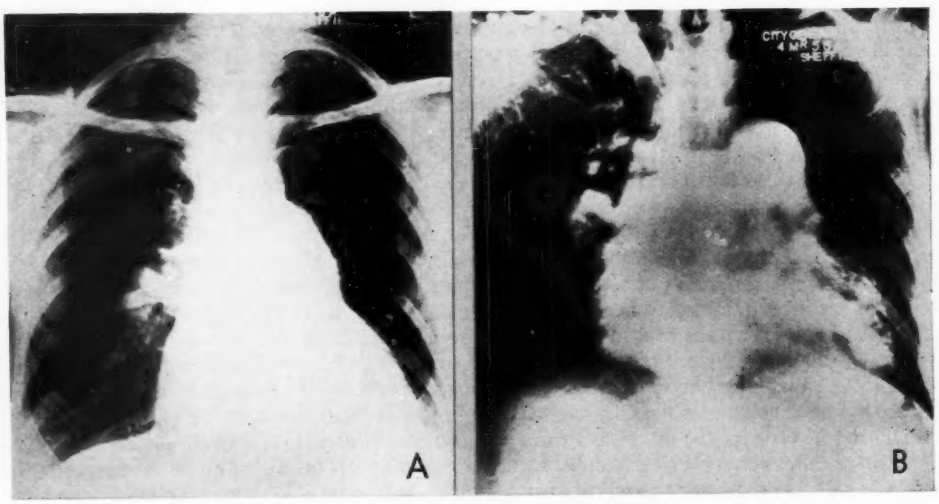

FIG. 2.—(A) Postero-anterior teleradiogram, showing moderate overall cardiac enlargement with prominence of the pulmonary trunk and its main branches. (B) Postero-anterior angiocardiogram taken 8 seconds after injection of the contrast medium, showing the retention of the dye in the dilated pulmonary arteries. The peripheral lung fields are unusually clear in both. Case 1.

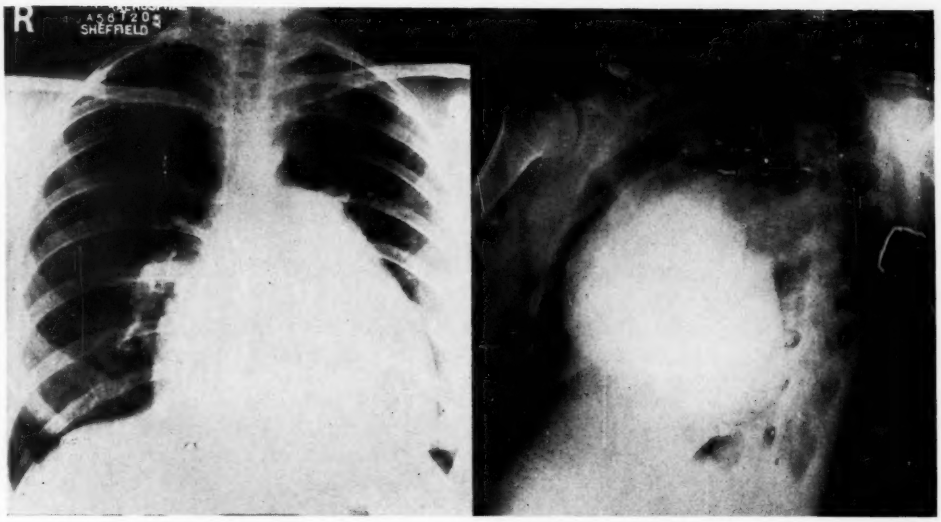

FIG. 3.—P-A teleradiogram and L.A.O. radiogram of the chest. The P-A view shows overall cardiac enlargement with prominence of the pulmonary trunk and its main branches. The peripheral lung fields are unusually clear. In the oblique view there is unusual prominence of the anterior border suggesting right ventricular hypertrophy. The overlapping of the spine by posterior border is suggestive of left ventricular hypertrophy. Case 4.

none was the media taken to be hypertrophied as in none did its thickness exceed 15 per cent of the external diameter of the vessel (Fig. 5). In Cases 1, 2, and 3 the weight of the heart was increased, due to right ventricular hypertrophy. The right chambers of the heart and the pulmonary artery were dilated. In each instance there was atheroma of the pulmonary arterial tree.

Other features of each case are described separately.

Case 1. A woman, aged 45 years, with three children, who had been well until a year before, was admitted for breathlessness on exertion. A few weeks later she developed jaundice, ascites, and bilateral swelling of the ankles. She appeared slightly cyanosed and jaundiced and had the type of brown pigmentation on the face, especially on the forehead, that is generally associated with tricuspid disease. The systemic blood pressure was 140/90 mm. The jugular venous pressure was raised about 14 cm. above the sternal angle and showed striking pulsation with a prominent *a* wave and a rapid *x* descent. At the mitral area a soft first sound was obscured by a systolic murmur which was followed by second and third heart sounds. At catheterization the pressures were: pulmonary artery 110/70 mm. Hg (mean 80), right ventricle 110/15 (mean 60), and right atrium 22/18 (mean 20). The hæmoglobin content was 14·2 g. per 100 ml. At autopsy the heart weighed 330 g. The thickness of the wall of the infundibulum of the right ventricle was 8 mm. and that of the sinus of the right ventricle 10 mm. The left ventricle was of normal size, its wall being 12 mm. thick.

Case 2. A boy, aged 13 years, complained of breathlessness on exertion, abdominal pain, and fainting attacks for only four months. There was no history of rheumatic fever. On examination he was not cyanosed. A loud systolic murmur was best heard in the third left intercostal space. The hæmoglobin level was 18·4 g. per 100 ml. At catheterization the pulmonary artery mean blood pressure was 70 mm. Hg. A month later he developed congestive cardiac failure and cyanosis. In spite of treatment with mercurial diuretics and paracentesis thoracis and abdominis on numerous occasions, he died two years after the onset of symptoms.

Case 3. A girl, aged 12 years, was admitted in congestive cardiac failure. At the age of 5 she developed breathlessness on exertion and became cyanosed. On examination there was cyanosis and finger clubbing. The systemic blood pressure was 130/80 mm. In the mitral area there was a thrill and a harsh systolic murmur, and in the pulmonary area the loud second sound was followed by a Graham Steell murmur.

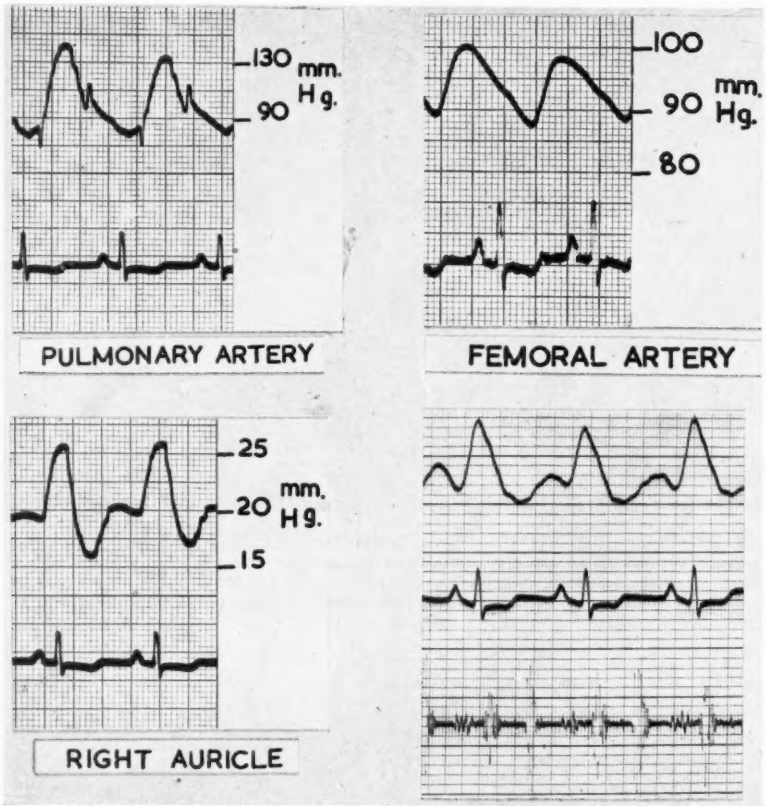

FIG. 4.—Tracings taken at cardiac catheterization and jugular phlebogram. *Upper left.* Pulmonary artery blood pressure tracing. *Upper right.* Femoral artery blood pressure tracing. *Lower left.* Right atrial blood pressure tracing, showing the giant presystolic *a* waves. *Lower right.* Synchronous recordings of jugular phlebogram, electrocardiogram (lead II), and phonocardiogram in the pulmonary area. The phlebogram shows prominent presystolic *a* waves. The peaked P waves suggest right atrial hypertrophy. The phonocardiogram shows a loud second sound and a triple rhythm. Case 4.

Cardiac catheterization was not performed. There was a disappointing response to mersalyl therapy and the patient, while still suffering from congestive cardiac failure, died suddenly.

The muscular pulmonary arteries (100–1000μ) were also grossly abnormal and showed healing medial necrosis (Fig. 5). In many vessels there were gaps up to 200μ in length in the media while in others there was loss of continuity of only the external elastic membrane. The lumen of many vessels was partially occluded by fibroelastic tissue which also occupied the gaps in the media to join with tubercles of fibrous tissue that bulged out into the lung parenchyma from the adventitia. The nuclei in the fibrous tissue in the medial deficiencies showed an unusual streaming effect with the long axes of the nuclei running in a radial direction. The adventitial tubercles, up to 400μ in diameter, consisted of loose cellular fibrous tissue containing many capillaries but no giant cells. The overall appearance was similar to that of the healing stage of periarteritis nodosa.

Case 4. A woman, aged 21 years, was admitted in congestive cardiac failure. At the age of 14 she began to get breathless on exertion and suffer from syncopal attacks. Her dyspnœa was progressive, and two years before admission she developed ankle swelling. There was no history of hæmoptysis but her

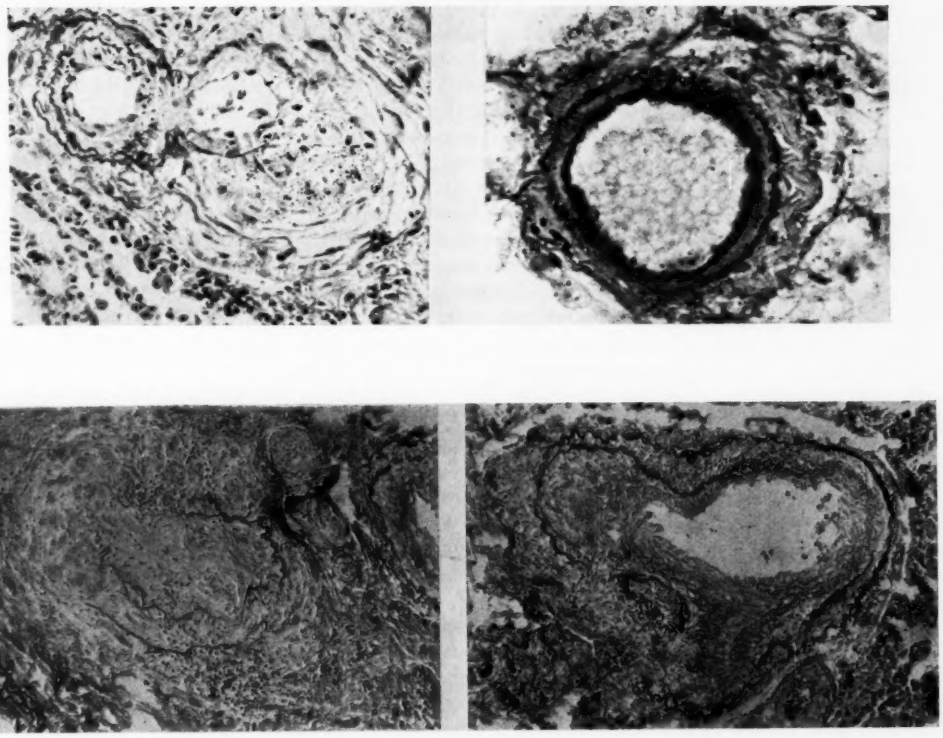

FIG. 5.—*Upper left*. Transverse section of pulmonary arteriole. The vessel is abnormal with a distinct muscular media between two elastic laminæ. Intimal fibrosis partially occludes the lumen. One sector of the vessel wall is necrotic and near this area is an adventitial mass of fibrous tissue. (Verhoeff/van Gieson's stains, × 300.) Case 3. *Upper right*. Transverse section of pulmonary arteriole. The vessel is abnormal with a distinct muscular media between two elastic laminæ. (Verhoeff/van Gieson's stains, × 500.) Case 2. *Lower left*. Transverse section of a muscular pulmonary artery. The media is necrotic and, while the internal elastic membrane can still be faintly seen around the entire circumference of the vessel, the faint external elastic membrane can be distinguished only in one sector of the vessel. The medial necrosis appears to have been subacute and extensive organization by fibrous tissue has occurred. The vessel is totally occluded by fibrous tissue and there is extensive adventitial fibrosis. There has been organization in the necrotic areas of the media. (Verhoeff/van Gieson's stains, × 52.) Case 3. *Lower right*. Transverse section of a muscular pulmonary artery. This vessel also shows organization following medial necrosis and the appearances are similar to the healing stage of periarteritis nodosa. In this case the changes are less severe. The lumen of the vessel is only partially occluded by fibrous tissue and the elastic membranes can be seen distinctly over a much wider area. (Verhoeff/van Gieson's stains, × 52.) Case 3.

friends had noticed that her voice was hoarse and that she appeared sunburned even in winter. On examination, her voice was hoarse and she had facial pigmentation and slight icterus but no central cyanosis. The systemic blood pressure was 100/80 mm. At the apex there was a presystolic triple rhythm and a systolic murmur which was conducted to the tricuspid area. Catheterization demonstrated the following blood pressures (Fig. 4): right atrium 25/15 mm. Hg (mean 20), right ventricle 150/20 mm. (mean 70), right pulmonary artery 145/85 mm. (mean 100), and pulmonary capillary 15 mm. (mean). The femoral artery blood pressure was 95 mm. The femoral artery blood oxygen saturation was 97 per cent and the mixed venous blood oxygen saturation was 50 per cent. The hæmoglobin level was 14·8 g. per 100 ml. and the hæmatocrit was 54 per cent. A renal clearance test demonstrated the renal plasma flow to be 99 ml./min. and the glomerular filtration rate 47 ml./min. Respiratory function tests were normal.

Discussion

Most of the reported cases of idiopathic pulmonary hypertension have been in young females. Case 2 of the present series and the patient reported by Brinton (1950) were male. Dresdale *et al.* (1951) stated that the disease has been reported at ages varying from 20 months (Cross and Kobayshi, 1947) to 80 years (McCallum, 1931).

Symptoms. Breathlessness on exertion, chest pain of anginal type, cough, blueness of the lips and nails, and abdominal distension and ankle swelling, due to congestive heart failure, are common symptoms in patients with idiopathic pulmonary hypertension. Hæmoptysis, hoarseness, syncopal attacks, palpitation, and jaundice occur less frequently. Most of these symptoms also occur in patients with other diseases where there is severe pulmonary hypertension so that they appear to be characteristic of this complication and are probably related to the anatomical abnormalities induced in the pulmonary vessels by the raised blood pressures. Breathlessness on exertion was the dominant symptom in all the present patients and in those described by previous authors. From a histological study of the pulmonary arteries in a child of 11 months with Eisenmenger's complex Edwards (1953) believed that the onset of dyspnœa was related to the development in the pulmonary arteries of intimal changes caused by the pulmonary hypertension. It seems possible that the progressive dyspnœa that occurs with other types of heart disease associated with pulmonary hypertension including idiopathic pulmonary hypertension is also due to anatomical changes in the pulmonary vessels which occur in the pulmonary vessels in all these patients.

Although hæmoptysis is another symptom that is characteristic of severe pulmonary hypertension and has been described in patients with idiopathic pulmonary hypertension (Dresdale *et al.*, 1951), it is not common in this disease, and did not occur in any of the present patients. It is possible, as suggested by Wood (1952), that the thin-walled pulmonary capillaries and veins are protected from the high pulmonary artery blood pressures by the anatomical changes that develop in the pulmonary arterioles and muscular pulmonary arteries in this condition.

A history of chronic cough and colds is very characteristic of patients with idiopathic pulmonary hypertension and was obtained in all the present series. These symptoms commonly occur with other diseases associated with pulmonary hypertension. Evans (1951) believed that a frequent cough was a factor that caused the disease to progress, since he thought that the rise in pulmonary artery blood pressure with coughing accelerated the development of intimal fibrosis over areas of medial aplasia and hypoplasia in the muscular pulmonary arteries.

Syncopal attacks have been reported in patients with idiopathic pulmonary hypertension (Wood, 1952; and Branwood, 1954) and these were associated with palpitation in patients reported by Werkö and Eliasch (1952) and Dresdale *et al.* (1951).

Although chest pain occurred in none of the present series it is a common symptom in patients with idiopathic pulmonary hypertension (Wood, 1952; Gilmour and Evans, 1946; and Branwood, 1954). Like dyspnœa, this symptom occurs in other forms of congenital heart disease associated with pulmonary hypertension (Hultgren *et al.*, 1953). Dresdale *et al.* (1951), although they found no associated coronary disease, thought that the chest pain was due to the coronary blood flow being insufficient for the degree of right ventricular hypertrophy in these patients, because it resembled angina pectoris so closely. Viar and Harrison (1952) noted that nitroglycerine had no effect on the chest pain associated with pulmonary hypertension and suggested that it was due to distension of the main pulmonary arteries.

Brinton (1950) described a man of 26 years with idiopathic pulmonary hypertension who had lost his voice due to paralysis of the left vocal cord which was probably caused by pressure on the recurrent laryngeal nerve by the grossly dilated pulmonary arteries. This type of hoarseness has also been reported in other patients with presumed severe pulmonary hypertension and extreme dilatation of the pulmonary arteries (Baumgartner and Abbott, 1929; and Millman and Kornblum, 1936).

Congestive cardiac failure is the usual terminal stage of idiopathic pulmonary hypertension. Although jaundice and facial pigmentation, which occurred as presenting symptoms in our Case 1,

have not been stressed in previous reports these signs might be expected to develop commonly as complications of congestive heart failure. They are probably manifestations of Shattuck's sign and are caused by hepatic distension associated with tricuspid incompetence.

Signs. The physical signs are those of right ventricular hypertrophy and pulmonary hypertension. In a recent review Bedford (1951) described a systolic impulse sometimes with a thrill, followed by a diastolic click corresponding to the second sound, palpable in the second and third left interspaces, a duplicated second sound, frequently a systolic murmur, occasionally a Graham Steell murmur, displacement of the apex beat to the left, a diffuse cardiac impulse, a triple rhythm and, later, signs of tricuspid incompetence as the important clinical signs of pulmonary hypertension: Wood (1952) has emphasized the diagnostic importance of giant *a* waves in the jugular venous pulse of patients with idiopathic pulmonary hypertension. Although many authors have commented only on the loudness of the second sound in the pulmonary area in patients with pulmonary hypertension, in the present series there was close splitting of the loud second sound in the pulmonary area such as was noted by Wood (1952). Although these signs are characteristic of idiopathic pulmonary hypertension they are not pathognomic of this disease since they have been described in patients with severe pulmonary hypertension complicating mitral stenosis or right-to-left shunts and constitute a group that Heath and Whitaker (1956) have termed hypertensive pulmonary disease.

Cyanosis occurs commonly as a terminal feature and in the absence of an intracardiac shunt has usually been considered to be of peripheral origin. However, Ordway (1952) found arterial oxygen unsaturation in a patient with idiopathic pulmonary hypertension during inhalation of pure oxygen which suggests that the anatomical changes in the small pulmonary vessels may sometimes cause impairment of aeration of the pulmonary arterial blood. All three patients in the present series appeared cyanosed but in those where the arterial blood oxygen was estimated, normal values were obtained.

There are no cardiac murmurs characteristic of idiopathic pulmonary hypertension. In the present series an apical systolic murmur occurred in all four cases, a basal systolic murmur in Case 2, and a Graham-Steell murmur in Case 3 but, as pointed out by Whitaker *et al.* (1955) these auscultatory signs are indistinguishable from those occurring when severe pulmonary hypertension complicates other congenital anomalies. In the terminal stage of idiopathic pulmonary hypertension congestive heart failure and tricuspid incompetence have been commonly noted and occurred in all the present cases. At this stage jaundice and pigmentation of the face may appear as in our Cases 1 and 4.

Wood (1952) considers that in idiopathic pulmonary hypertension the peripheral pulse is small and the blood pressure rather low with the systolic and diastolic pressure approaching the mean. In our Case 4 the radial pulse was of poor volume and the systemic blood pressure was 100/80, which was lower than the pulmonary artery blood pressure.

Electrocardiography. The electrocardiogram shows evidence of right ventricular hypertrophy and usually there is also evidence of right atrial hypertrophy (Howarth *et al.*, 1947; and Wood, 1952) (Fig. 1). While these signs are characteristic of idiopathic pulmonary hypertension they are not pathognomonic of it since, like many of the symptoms and signs, they occur with mitral stenosis and right-to-left shunts complicated by severe pulmonary hypertension.

Radiology. In patients with idiopathic pulmonary hypertension radiological examination usually shows dilatation of the pulmonary artery and its main branches with increased pulsation not amounting to a hilar dance, abnormally clear peripheral lung fields, and cardiac enlargement that is due to right ventricular hypertrophy but may suggest left ventricular hypertrophy, as in Cases 1 and 4 (Fig. 3). These features are found in other forms of heart disease complicated by severe pulmonary arterial hypertension and often mask other abnormal radiological signs that occur with these diseases (Brown *et al.*, 1955; Whitaker *et al.*, 1955; and Heath *et al.*, 1956). It is impossible to differentiate idiopathic pulmonary hypertension from ventricular septal defect, atrial septal defect, or patent ductus with pulmonary hypertension by examination of teleradiograms.

Patients with mitral stenosis with severe pulmonary hypertension, who may show clinical and cardiographic features identical with those of idiopathic pulmonary hypertension can usually be distinguished on radiological examination by the degree of left atrial enlargement, pulmonary hæmosiderosis, and horizontal lines at the lung bases due to lymph stasis (Whitaker and Lodge, 1954).

Angiocardiography. As in all patients with severe pulmonary hypertension, angiocardiography demonstrates dilated main pulmonary arteries and a coppicing effect in the peripheral lung fields (Fig. 2). This method is not of diagnostic importance in patients with idiopathic pulmonary hypertension unless they have central cyanosis when demonstration of the absence of an abnormal shunt from the right chambers of the heart excludes conditions such as patent ductus, atrial septal defect, and ventricular septal defect with reversal of flow.

Cardiac Catheterization. In patients with idiopathic pulmonary hypertension who have been studied by catheterization (Howarth *et al.*, 1947; Dresdale *et al.*, 1951; Werkö and Eliasch, 1952; and Wood, 1952) it has been possible to demonstrate severe pulmonary arterial hypertension (Fig. 4), normal pulmonary capillary blood pressure, abnormally high atrial pulse pressures (Fig. 4), normal or only slightly reduced arterial blood oxygen saturation, and abnormally low mixed venous blood oxygen saturation indicating an increased arterio-venous oxygen difference and a low cardiac output. Cardiac catheterization is the most important method of special investigation since it distinguishes patients with congenital cardiac anomalies such as patent ductus, atrial septal defect and ventricular septal defect with severe pulmonary arterial hypertension and balanced shunts who are clinically indistinct from patients with idiopathic pulmonary hypertension. In the anomaly under discussion the blood samples show no evidence of an intracardiac shunt while in these other congenital anomalies, even when the flows appear balanced from clinical examination, it is usual to detect some change in the oxygen saturation of samples from the right side of the heart, and is usually possible to direct the tip of the catheter through a ductus or a septal defect (Whitaker *et al.*, 1955).

Other Investigations. Pulmonary function has not been extensively studied in idiopathic pulmonary hypertension. Dresdale *et al.* (1951) studied the ventilatory capacity in two of their patients and found it to be normal in one and reduced in the other. In Case 4 of the present series respiratory function was normal. Werkö and Eliasch (1952) found a low glomerular filtration rate and a low renal blood flow in a patient with idiopathic pulmonary hypertension, and these and the renal plasma flow were extremely low, about a sixth of their normal value, in our Case 4.

Pathology. Anatomical abnormalities in the heart and lungs that characterize idiopathic pulmonary hypertension are hypertrophy and dilatation of the right ventricle, dilatation of the tricuspid ring, right atrial hypertrophy, dilatation of the pulmonary valve and main pulmonary arteries, with pulmonary atheroma and specific changes in the small pulmonary vessels. None of these anatomical abnormalities is pathognomonic of idiopathic pulmonary hypertension since all may occur when severe pulmonary hypertension complicates cases with a left-to-right shunt.

The most common abnormality in the small pulmonary blood vessels is a distinct muscular media in the pulmonary arteriole ($<100\mu$ in diameter), which normally, in the adult, consists of a single elastic lamina lying between intima and adventitia. This abnormality was present in all three cases examined at autopsy in this series, and in Cases 1 and 3 there was also intimal fibrosis leading to occlusion of the lumen of the arterioles. Usually there is also medial hypertrophy in the muscular pulmonary arteries (100–1000μ in diameter) and intimal fibrosis which may completely occlude the lumen of these vessels. Medial necrosis sometimes occurs in the muscular pulmonary arteries and pulmonary arterioles and was observed in Cases 1 and 3. These anatomical abnormalities have been described frequently in idiopathic pulmonary hypertension (Howarth *et al.*, 1947; Werkö and Eliasch, 1952; Aitchison and Richmond, 1955; Gilmour and Evans, 1946; and Branwood, 1954) but with the exception of arterial necrosis have been reported equally commonly in other diseases associated with severe pulmonary arterial hypertension.

Differential Diagnosis. The differential diagnosis of the present anomaly is from other cyanotic

and acyanotic conditions associated with pulmonary hypertension. Cyanosis in idiopathic pulmonary hypertension is rarely so severe as in patients with septal defects, patent ductus, or transposition, associated with pulmonary hypertension in whom the degree of polycythæmia may be so severe as to mimic polycythæmia rubra vera (Whitaker *et al.*, 1955). A long history of recurrent pulmonary infection and signs of pulmonary hypertension and cyanosis may suggest chronic pulmonary heart disease but the absence of carbon-dioxide retention will exclude this diagnosis (Platts and Whitaker, 1954). Since the clinical, radiological, and electrocardiographic features of cases with left-to-right shunts and pulmonary hypertension may be indistinguishable from idiopathic pulmonary hypertension, these lesions are difficult to differentiate from it unless angiocardiography and cardiac catheterization are carried out. Angiocardiograms show no intracardiac shunt in idiopathic pulmonary hypertension but often demonstrate early filling of an overriding aorta in Eisenmenger's complex (Brown *et al.*, 1955), early filling of the descending aorta from the pulmonary artery in patent ductus arteriosus (Whitaker *et al.*, 1955), early filling of the left atrium in atrial septal defect (Whitaker *et al.*, 1955), and early filling of the left ventricle in ventricular septal defect, when these anomalies are associated with pulmonary hypertension of such a degree as to cause reversal of the flow. After studying patients with congenital septal defects complicated by severe pulmonary hypertension, who on clinical, radiological, and cardiographic examination had appeared indistinguishable from patients with idiopathic pulmonary hypertension, the present authors thought that the latter diagnosis could be substantiated only when autopsy proof was available (Whitaker *et al.*, 1955). However, it now seems that cardiac catheterization usually reveals underlying congenital cardiac anomalies, when they are present, and that, if at this investigation it has not been possible to pass the catheter through a ductus or a septal defect or to demonstrate an intracardiac shunt from an examination of the oxygen saturation of the blood samples from the heart, idiopathic pulmonary hypertension may generally be diagnosed.

Prognosis and Treatment. Although patients may have symptoms of breathlessness for many years, as in Case 4 of the present series, the disease runs a malignant course after the onset of congestive cardiac failure and death usually occurs within two years, as in the other cases of this series and in the patient reported by Aitchison and Richmond (1955).

No treatment that has any significant influence on the course of idiopathic pulmonary hypertension has been described. Repeated oxygen inhalation (Motley *et al.*, 1947; Swan and Wood, 1954) and antispasmodics, especially priscoline (Dresdale *et al.*, 1951) have been used in attempts to overcome any possible pulmonary vascular spasm. However, it seems unlikely that such treatment can alleviate a disease that is characterized by severe abnormalities in the small pulmonary blood vessels which, on histological appearances, appear to be irreversible. Prolonged anticoagulant therapy suggested by Cutler *et al.* (1954) seems unlikely to have any effect on the disease since most of the pulmonary blood vessels are totally occluded by proliferation of intimal fibro-elastic tissue not secondary to thrombi. Furthermore, in patients who have had severe hæmoptyses it may be dangerous. There is no satisfactory surgical treatment for idiopathic pulmonary hypertension and it should be regarded as a fatal disease characterized by irreversible occlusive changes in the small pulmonary blood vessels not amenable to any form of treatment.

Summary

One boy, one girl, and two women with idiopathic pulmonary hypertension are described. The diagnosis was confirmed at autopsy in three and the other is still alive.

The symptoms and signs associated with this anomaly are characteristic but not pathognomonic since they occur in other forms of heart disease with severe pulmonary hypertension. Breathlessness on exertion, chest pain of anginal type, cough, blueness of the lips and nails, and abdominal distension and ankle swelling due to congestive cardiac failure are common symptoms in patients with idiopathic pulmonary hypertension. Hæmoptysis, hoarseness, syncopal attacks, palpitation, and jaundice occur less frequently.

The only physical signs common to the group of patients are those of pulmonary hypertension and congestive cardiac failure. There is always electrocardiographic evidence of right ventricular dominance.

On radiological examination there is moderate to great cardiac enlargement, dilatation of the pulmonary artery and its main branches, and clear peripheral lung fields. These features are not sufficiently characteristic to distinguish them from severe pulmonary hypertension complicating other cardiac anomalies.

Angiocardiography is of diagnostic importance only when there is central cyanosis. Cardiac catheterization is considered the most important diagnostic investigation since it demonstrates the absence of intracardiac shunts.

The pathological features and histological abnormalities in the small pulmonary blood vessels in three cases are described.

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SOLITARY PULMONARY HYPERTENSION

BY

WILLIAM EVANS, D. S. SHORT,* AND D. EVAN BEDFORD

From the London, Middlesex, and National Heart Hospitals

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An increased resistance to the pulmonary circulation in chronic lung disease has long been known as a cause of right ventricular enlargement, and Graham Steell (1888) described functional pulmonary incompetence due to high pressure in the pulmonary artery in mitral stenosis. The modern conception of pulmonary hypertension was introduced by Moschowitz (1927) who was the first to recognize it in various forms of heart disease, in chronic lung disease, and in pulmonary arterial disease, and to describe its clinical signs. The advent of cardiac catheterization has enabled us to test the clinical signs identified with pulmonary hypertension, to measure its severity, and to discover conditions like congenital cardiac or vascular fistulæ that may be associated with it.

We may define pulmonary hypertension as a persistent elevation of pulmonary arterial pressure sufficient to cause enlargement and ultimately failure of the right ventricle. The diagnosis rests on the clinical, electrocardiographic, and radiological findings.

It is expedient to divide pulmonary hypertension into four distinct clinical groups. In the *first* group the pulmonary hypertension is associated with chronic lung disease like emphysema, congenital cystic disease, and anthracosis. In the *second* group it is associated with heart disease like mitral stenosis or certain congenital cardiovascular defects. In a *third* group, it is caused by obstructive pulmonary arterial lesions such as recurring embolism, bilharzial endarteritis, neoplasm, or periarteritis nodosa. In the *fourth* group of patients, hypertensive pulmonary vascular disease is an isolated finding.

It is with this last group that our present paper deals and we describe 11 cases of solitary pulmonary hypertension in the sense defined, all of which were examined clinically and at necropsy; this and subsequent histological examination proved the absence of disease of the lung parenchyma and of any heart disease other than right ventricular hypertrophy, so confining the cause of pulmonary hypertension to the lesser pulmonary arteries. The clinical diagnosis of pulmonary hypertension is no longer difficult, and it is from a careful pathological examination that knowledge of the condition will increase. It has been our purpose, therefore, to describe in some detail the pathological findings in our 11 patients and to search in them for an explanation of the pulmonary hypertension which had in turn given rise to enlargement and failure of the right ventricle and ultimately to the demise of the patient.

The Method of Investigation. A routine clinical, electrocardiographic, and radiological examination was made in all 11 patients, and cardiac catheterization was performed in 7 of them. At necropsy the heart was weighed and the degree of right ventricular hypertrophy estimated by measuring the thickness of its wall and comparing it with that of the left ventricle. Sometimes the free wall of each ventricle was weighed after separation at the septum.

Special attention was paid to the lung and its vasculature. After opening the pulmonary trunk to exclude the presence of massive embolism, the lungs were removed and one was usually preserved intact for arteriography. The perfusion material used to obtain this *pulmonary arteriogram* was bismuth oxychloride in gelatine, and the technique devised by Shillingford at the London Hospital

* Holding a Leverhulme Research Scholarship.

was followed. Injection of the bronchial arteries in cases outside this series failed to yield additional information of value. The lung, usually inflated to life-size following the injection, was subsequently radiographed in both postero-anterior and lateral projections and also stereoscopically. The radiograph was then magnified, using a fine grain film so that the arterioles were rendered visible as far as vessels of 0·03 mm. in diameter (Short, 1956).

After fixation in formalin, sections of the injected lung were taken for histological examination, and particularly from places where the arteriogram indicated interruption of the circulation. As a rule, five samples were removed for microscopy from each lung, including at least one block from each lobe. The sections were stained with either Hart or Verhoff elastic stains combined with Van Gieson, as well as with hæmatoxylin and eosin; sometimes serial sections were examined in this way.

Age and Sex

The youngest of our 11 patients was aged 7 and the oldest 64 years at death; of the remainder, four were from 20 to 29 and five from 30 to 39 years. Brenner (1935) stated that primary pulmonary vascular disease occurred mostly in childhood, adolescence, and early adult life, and certainly the majority of authentic cases are under 40 years of age. The disease is now being recognized more often in children and Berthrong and Cochran (1955) have reported the condition in 9 children all examined at necropsy.

All our patients were female. Earlier statistics (Brenner, 1935; Brill and Krygier, 1941) gave the sex incidence as even, but Dresdale *et al.* (1951) found that 60 per cent of reported cases were female, and in recent papers a female predominance is still more evident.

Symptoms

Dyspnœa. The first and dominant symptom was dyspnœa. Sometimes this developed unexpectedly during exercise or after some trivial illness; sometimes it came on more gradually. Once appreciable dyspnœa had developed, it usually increased rapidly until eventually even slight effort provoked distressing breathlessness, often accompanied by oppression in the chest and a sense of choking and by faintness or exhaustion. Six of our patients developed orthopnœa, and five had paroxysms of dyspnœa often associated with chest pain, faintness, or even brief syncope. In these attacks the pulse was rapid and very small, and cyanosis became accentuated.

Cardiac Pain. Pain of anginal type and distribution occurred in 6 patients. Sometimes it was provoked by effort and sometimes it occurred at rest or at night, but always it was associated with dyspnœa and this distinguished it from the usual form of coronary pain. One patient, aged 64, who for five years had been subject on exertion to constricting upper chest pain extending into both arms and associated with dyspnœa, had a severe attack, lasting ten minutes and accompanied by syncope, that was diagnosed at the time as coronary thrombosis. Another patient subject to effort pain later developed paroxysms of dyspnœa with constrictive pain lasting ten minutes, sometimes accompanied by vomiting.

Angina pectoris in pulmonary vascular disease was recognized by Posselt (1908) and by Vaquez and Giroux (1908) who named it hypercyanotic pulmonary angina, and this term was also adopted by Arrillaga (1912) in his original account of Ayerza's disease. An identical form of angina occurs in pulmonary hypertension associated with mitral stenosis or with congenital intracardiac shunts. In these conditions also, it is associated with dyspnœa, and when provoked by effort it tends to subside slowly with rest.

Viar and Harrison (1952) discussed this form of cardiac pain and suggested that it arose from distension of the pulmonary artery. Stuckey (1955) specially investigated its pathogenesis and concluded that it was essentially related to a severely restricted cardiac output and a high pulmonary vascular resistance, with an inadequate coronary flow on effort. The exercise electrocardiogram showed ischæmic changes and we have confirmed this. Cyanosis, if present, may be intensified, but the hall-mark of pulmonary angina is dyspnœa rather than cyanosis.

Syncope. Five of our patients had syncopal attacks, sometimes provoked by effort, sometimes associated with paroxysms of dyspnœa or pain, and sometimes repetitive. Howarth and Lowe (1953) found that, in primary pulmonary hypertension, the pulmonary arterial pressure rose steeply with effort, after which the right ventricular output fell and its diastolic pressure rose, so that they postulated an acute right ventricular failure as the cause of syncope. Both pain and syncope may occur in the same patient, and there can be no doubt that both are symptoms of a restricted cardiac output. Exhaustion and weakness on effort are lesser symptoms from the same cause.

Physical Signs

Those patients seen at the start of their illness showed little or no cyanosis at rest, though it was sometimes present during exertion. Later, cyanosis sometimes became conspicuous especially during paroxysms of dyspnœa. Arterial anoxæmia was rarely sufficient by itself to account for cyanosis so that a low cardiac output and polycythæmia were mostly responsible for it. Clubbing of the fingers was absent in all but one, where it was slight.

The pulse was usually small or became so later and was sometimes impalpable. Auricular fibrillation was never observed. The blood pressure was usually normal or low when first recorded, and invariably low in the later stages: in two patients, the initial blood pressure was slightly raised. In six cases, the jugular venous pulse exhibited a prominent or even occasionally a giant auricular wave; with the onset of congestive failure, this wave became less obvious and was often overshadowed by the systolic wave of tricuspid incompetence.

Palpation almost always provided evidence of right ventricular hypertrophy. The apex beat, sometimes displaced to the left, was of right ventricular type. A systolic lift over the conus arteriosus was usual, and occasionally there was a widespread systolic impulse from sternum to apex, but in general this pulsation was less widespread and less forcible than that observed in cases of atrial septal defect. A diastolic shock synchronous with pulmonary valvular closure was often present.

A constant finding on auscultation was a loud pulmonary second sound, present in all cases but one, where it was obscured by a loud diastolic murmur. Generally, the second sound at the pulmonary area was obviously but closely split, the second or pulmonary element being the louder. A pulmonary early systolic click or ejection sound (Lian, 1940; Leatham and Vogelpoel, 1954) was heard in six cases, sometimes followed by a systolic murmur which was never loud. A blowing diastolic murmur of pulmonary incompetence was present at some stage in four cases. An apical systolic murmur was heard in several, which may have been of tricuspid rather than mitral origin. A triple rhythm at the apex or over the right ventricle was noticed in 6 cases; usually it was due to a third heart sound, but occasionally to an auricular sound. Once (Case 1) a sound that resembled a mitral opening snap was heard in early diastole.

Special Investigations

Blood Examination. Slight polycythæmia was present in 8 of the 9 where a blood count was recorded, the highest red cell count being 8·8 million and the highest hæmoglobin 140 per cent. A polymorphonuclear leucocytosis occurred in four, the highest white cell count being 18,900 per c.mm. The Wassermann reaction was always negative. The arterial oxygen saturation, recorded in six cases, varied from 63 to 93 per cent, being usually between 84 and 93 per cent. The cause of this arterial anoxæmia has not been adequately explained: it was not due to a patent foramen ovale, for this was only present in two cases, and in one of them the aperture merely admitted a probe; it may have been caused by a shunt through the enlarged broncho-pulmonary anastomoses.

Radiological Examination. In the anterior view, the right atrium was enlarged in 9 cases, and enlargement towards the left, interpreted as due to the right ventricle, occurred in 10 cases. Right ventricular enlargement involving the conus gave a blunted or square shape to the left heart contour compared with the more pointed oval of left ventricular enlargement. The pulmonary trunk was dilated in every case; it was aneurysmal in 3, much enlarged in 4, and merely prominent in 4 cases. The aorta, in the anterior view, appeared relatively small in 9 and normal in 2 cases.

The main pulmonary branches were enlarged in 9 and normal in 2 cases. The peripheral lung fields were oligæmic in 8, and never plethoric. The large hilar vascular shadows often faded abruptly so that the distal arterial branches appeared unduly narrow (Fig. 1 to 4). One case showed the scar of a pulmonary infarct but no others showed any evidence of disease of the lung parenchyma.

Electrocardiogram. The electrocardiogram always presented unequivocal evidence of right ventricular hypertrophy. The standard leads always showed right axis deviation combined with T wave inversion in leads III and II in 7 cases. Lead V1 or CR1 always showed a dominant R wave and a negative T wave except once when it was flat. Large and usually sharply pointed P waves in leads II, or II and III, were seen in 9 cases, and usually the P waves were also large in the right chest leads. There was always normal sinus rhythm (Fig. 5 and 6).

The *phonocardiogram*, when recorded, confirmed the auscultatory findings (Fig. 7). Splitting of the second sound was narrow as a rule, with accentuation of the pulmonary component. When a pulmonary systolic murmur was recorded its bulk was in mid-systole and it ended before reaching the pulmonary second sound. The start of the murmur was sometimes signalled by the early systolic ejection sound. Once the phonocardiogram showed a high frequency sound in early diastole (Fig. 7D).

Cardiac Catheterization. Solitary pulmonary hypertension cannot be diagnosed with certainty unless the presence of a congenital intra-cardiac fistula has been excluded. For this purpose direct exploration of the cardiac septa and of the ductus arteriosus by catheter is necessary, and even this is not always conclusive; blood-gas analysis cannot exclude a balanced shunt. For this reason we have omitted from our present series a number of cases in which the diagnosis of solitary pulmonary hypertension was supported by catheterization, and have restricted it to those cases proved by necropsy.

The pulmonary artery pressure was recorded in 6 cases of this series and it was always considerably raised, being 118/80, 70/40, and 67/25 mm. in 3 cases, and in the other 3 the mean pressure was 107, 74, and 63 mm. respectively. In another case the right ventricular mean pressure was 47 mm. The pulmonary capillary pressure was never raised and the cardiac output when measured was low.

Clinical Course

Sometimes the onset of dyspnœa was quite abrupt. Thus, in one patient it started with a breathless attack while alighting from a bus, in another it followed an attack of bronchitis, and two patients, accustomed to vigorous exercise, found themselves unexpectedly incapacitated at tennis and hockey. Tightness in the chest, cyanosis, fatigue, faintness or syncope were soon linked to dyspnœa on exertion.

Once overt dyspnœa had occurred, it progressed rapidly, activity became much restricted and, when cyanosis at rest was evident, effort of any sort provoked extraordinary distress. Orthopnœa, paroxysms of dyspnœa with intense cyanosis, chest pain, and occasionally repeated syncope with a small or impalpable pulse characterized the final stages of the disease.

In 10 cases in which the date of onset of symptoms could be determined, the subsequent span of life varied from five months to seven years, the average being approximately 2½ years. The shortest survival was in the youngest patient, aged 7, and the longest in the oldest patient, aged 64. Case 9 was exceptional in that a cardiac murmur had been noticed in childhood, syncopal attacks on effort began at the age of 16, severe dyspnœa with chest pain at the age of 26, and she died during pregnancy, aged 27. Necropsy showed congenital aneurysmal dilatation of the pulmonary artery in addition to pulmonary vascular disease.

Two patients died during pregnancy which had greatly aggravated their symptoms. Congestive heart failure appeared before death in 10 patients though in 5 of them death was sudden from syncope or peripheral circulatory failure. In three, a terminal state of drowsiness and apathy set in, and one patient died following an epileptic fit.

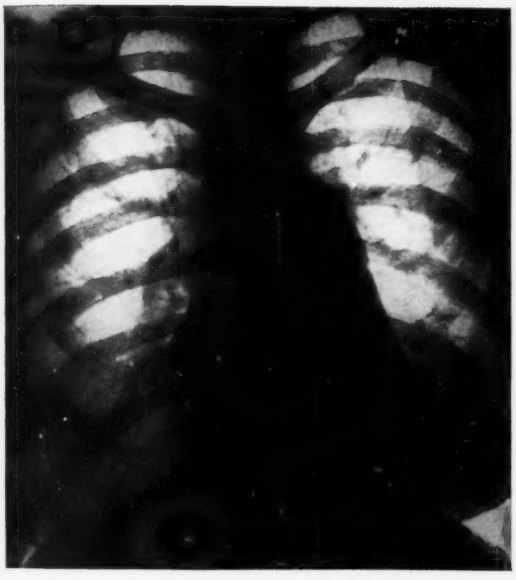

FIG. 1.—Moderate enlargement of the pulmonary artery and prominence of its main branches. Ischæmia of peripheral lung fields. Case 5.

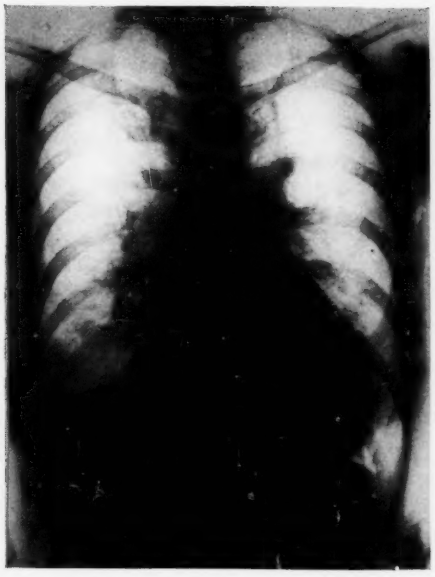

FIG. 2.—Moderate enlargement of the heart. Slight enlargement of the pulmonary artery and prominence of the main branches, but clear peripheral lung fields. Case 3.

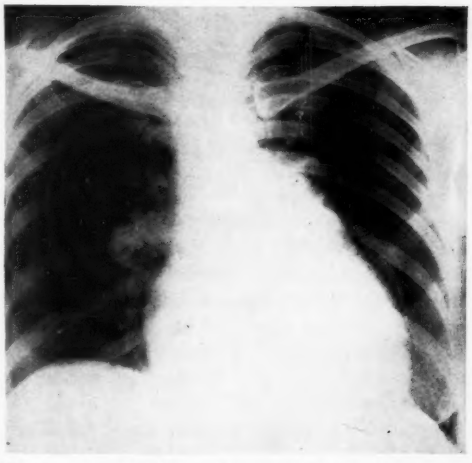

FIG. 3.—Considerable enlargement of the heart and of the pulmonary artery with prominence of the right main branch; ischæmia of peripheral lung fields. Case 6.

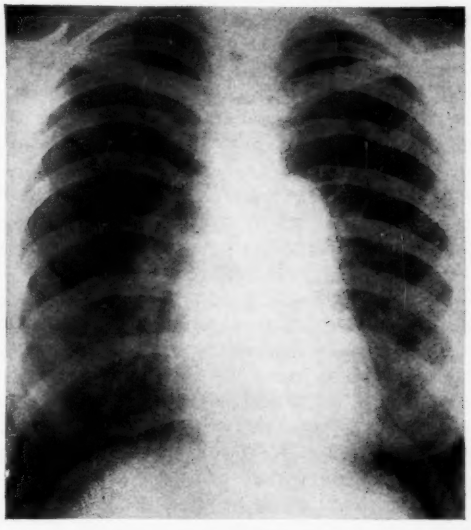

FIG. 4.—Slight enlargement of right atrium. Small aorta. Great prominence of pulmonary artery and less of its main branches. Secondary pulmonary branches visible, but ischæmia of peripheral lung fields. Case 4.

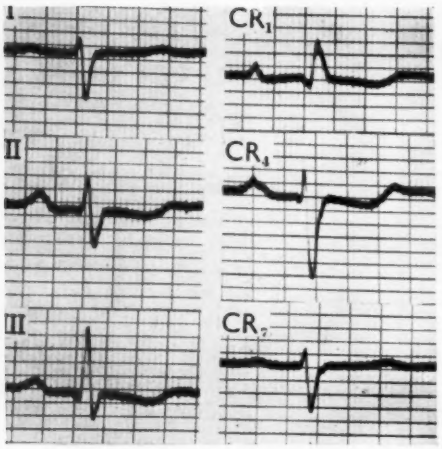

FIG. 5.—Right ventricular preponderance. Case 1.

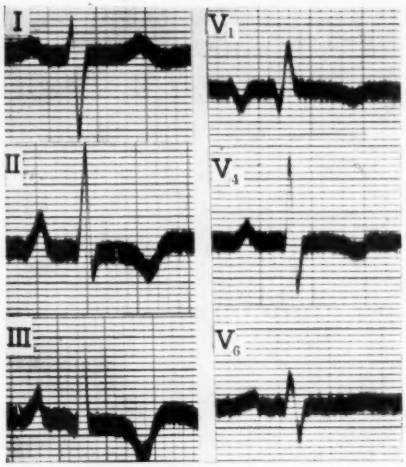

FIG. 6.—Right atrial and ventricular preponderance. Case 3.

DIAGNOSIS

The diagnosis of solitary pulmonary hypertension can only be made after all other varieties have been excluded. Usually it is not difficult to recognize chronic lung disease by its long and characteristic history and by its clinical and radiological signs. It causes manifest central cyanosis, often finger clubbing, and there may be an increased cardiac output with a full pulse and warm extremities.

Mitral stenosis is the commonest condition to be found in association with severe pulmonary hypertension and this may cause the customary murmurs to wane and even to disappear, although the opening snap persists as a rule. Rarely, the recognition of a snap sound in early diastole presents a difficulty as happened in our Case 1, when phonocardiography helped to decide. There is usually a long history of heart disease, and left atrial enlargement on radioscopy; an inconstant diastolic murmur may be detected by repeated auscultation. Apart from these differential features, severe pulmonary hypertension associated with mitral stenosis presents the same low cardiac output syndrome of anginal pain, faintness or syncope, peripheral cyanosis and small pulse, as occurs in the solitary form.

Difficulty in diagnosis may also arise when pulmonary hypertension is associated with congenital defects such as patent ductus arteriosus and intracardiac shunts, for the characteristic murmurs may disappear as the pressures in the two sides of the heart equalize and the shunt becomes balanced or even reversed. In expert hands the cardiac catheter can usually be passed through a widely patent ductus or an atrial septal defect, but clinical differentiation may be difficult, and Whitaker *et al.* (1955) have suggested that many cases diagnosed as idiopathic pulmonary hypertension are, in fact, cases of patent ductus. In most such cases, however, there is a history of heart disease recognized in childhood, finger clubbing is more common, and if the shunt is reversed, angiocardiography can show premature filling of the descending aorta from the pulmonary artery. Pulmonary hypertension associated with atrial septal defect cannot always be distinguished from the solitary type by clinical examination, but there is usually a longer history of heart disease or of cardiac symptoms, while cardiac catheterization should be diagnostic. Dexter (1956) regards cases of pulmonary hypertension with a small atrial septal defect as examples of primary pulmonary vascular disease.

Pulmonary hypertension and right heart failure due to repeated pulmonary embolism may be difficult or impossible to distinguish on clinical grounds from solitary pulmonary hypertension, and

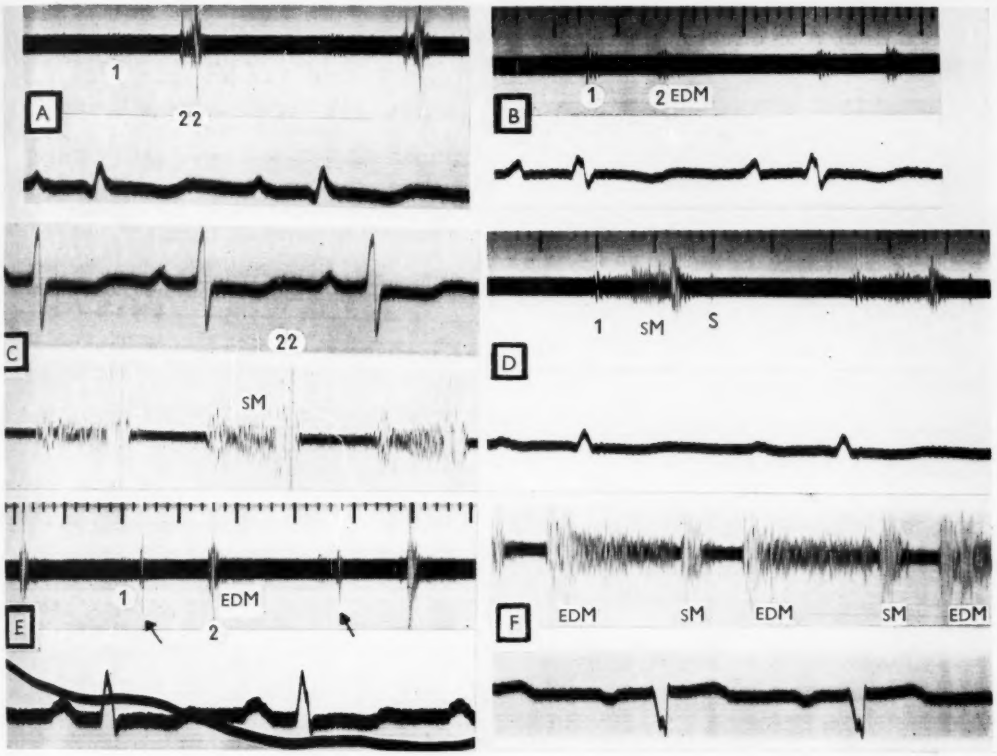

FIG. 7.—Representative phonocardiograms from our series. (A) Close splitting of second heart sound with accentuation of its pulmonary component. (B) Early diastolic murmur of pulmonary incompetence. (C) Systolic murmur ending at aortic component of closely split second sound whose pulmonary element is accentuated. (D) Sound in early diastole from Case 1. (E) Sound in early systole and an early diastolic murmur of pulmonary incompetence. (F) Long diastolic murmur of pulmonary incompetence and mid-systolic murmur which stops short of the second sound. The reference electrocardiogram is lead II in E and F, elsewhere CR1.

even at necropsy the distinction can be difficult, particularly when the small arteries are involved. In all forms of severe pulmonary hypertension with reduced cardiac output, thrombotic or even embolic occlusion of the larger pulmonary arteries is quite common, and only careful examination of the whole pulmonary vasculature can decide the primary lesion. As illustrative of this difficulty, we may mention two patients reported by Goedel (1930) in whom right heart enlargement and failure were associated with thrombotic lesions in the large pulmonary arteries and with intimal hyperplasia in the small arteries. Brenner (1935) included both of Goedel's cases in his group of primary pulmonary vascular sclerosis, and Brill and Krygier (1941) regarded them likewise, but Lenègre and Gerbaux (1952 and 1955), on the other hand, claimed them as examples of heart disease due to pulmonary arterial thrombosis. We also met this difficulty in three cases that, though regarded as having solitary pulmonary hypertension during life, were found at necropsy to have massive pulmonary embolism or thrombosis and systemic venous thrombosis.

In general, embolic or thrombotic pulmonary hypertension occurs at a later age than the solitary form, usually after 40, and episodes of pulmonary infarction, pleural effusion, or peripheral venous thrombosis can sometimes be recognized at the onset or from the history. In the later stages, when the thrombus has organized, the symptoms and signs may be indistinguishable from those

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of solitary pulmonary hypertension. Sometimes radioscopy shows immobility of the thrombosed hilar branches, or an abrupt amputation of a main branch beyond the seat of thrombosis.

Pathology

The liver, spleen, kidneys, and other systemic organs were usually the seat of chronic venous congestion and occasionally of infarction, but the most important changes were found in the heart and lungs. Cardiac malformations like atrial or ventricular septal defects and patent ductus arteriosus were naturally excluded in every case; there was valvular patency of the foramen ovale twice, one case admitting a probe and the other a pencil. The valves were always healthy; the coronary arteries were free from significant atherosclerosis, and there was no myocardial infarction.

The heart was heavier than normal except in one instance (Case 5). Sometimes the increase was slight, but occasionally the weight was three times the normal. In our 11 women patients it ranged between 250 and 525 g., with an average of 393 g. compared with the normal of about 250 g. Right ventricular hypertrophy, usually with moderate or greater dilatation, was invariably present, and the thickness of the ventricle varied from 7 to 20 mm. compared with 9 to 15 mm. for the left ventricle. Intracardiac thrombosis was present in two cases, involving the right auricle in one and the right auricle and ventricle in the other.

Fig. 8.—Pulmonary thrombosis or embolism complicating pulmonary hypertension in Case 7, aged 7 years. A thrombus is seen filling both main pulmonary arteries.

Fig. 9.—Pulmonary arteriogram from Case 1, showing absence of injected material from large areas caused by thrombotic occlusion of some of the segmental arteries. The dense blotches indicate areas of actual infarction.

The lung parenchyma usually appeared healthy on naked-eye examination apart from areas of infarction in two cases. The pulmonary arterial trunk was always dilated and so as a rule were its main branches in which intimal thickening was more widespread than usual in subjects of the same age. In two cases the trunk or a main branch was thrombosed (Fig. 8). The segmental arteries of 2 to 5 mm. diameter often stood out prominently from the cut surface of the lung. The bronchial arteries in their course to the lungs were never enlarged.

The *pulmonary arteriogram* clearly portrayed narrowing or occlusion wherever it occurred in the arterial tree. When the larger arteries were occluded by thrombus, the territory they supplied was devoid of opaque material leaving bare areas. In places of actual infarction, the injected medium collected to form irregular blotches which had a granular appearance in the full-sized film (Fig. 9). When the muscular arteries were occluded, they ended blindly, giving to the arteriogram a pruned appearance which has been likened to the denuded shrub in autumn replacing the leafy bush in spring (Evans, 1951) which is its normal appearance (Fig. 10 and 11).

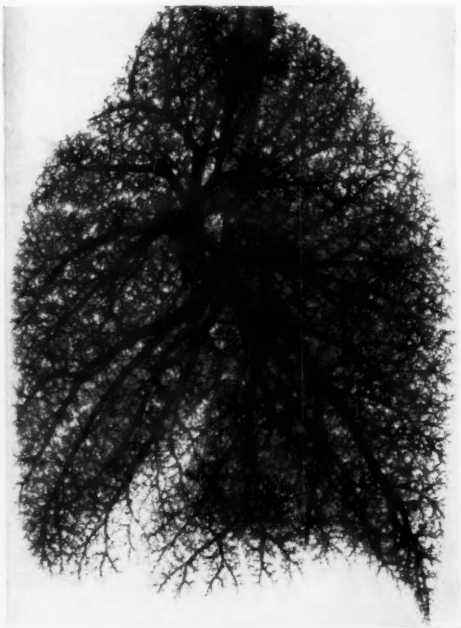

FIG. 10.—Normal pulmonary arteriogram.

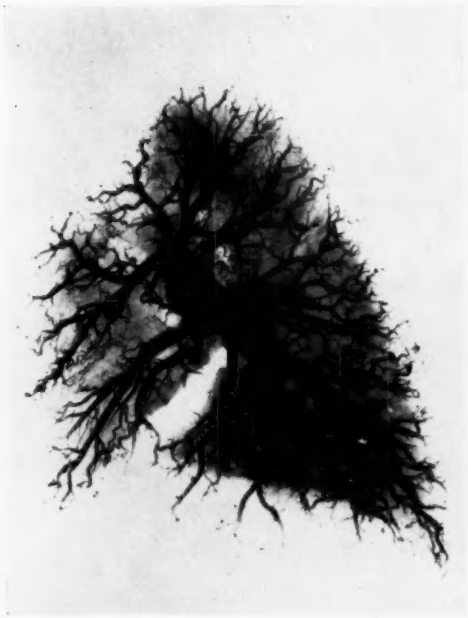

FIG. 11.—Pulmonary arteriogram from Case 4, showing pruning of the lobular vessels following occlusion of many muscular arteries.

When the arterioles were occluded there was obvious impoverishment of the fine tracery at the periphery of the magnified arteriogram (Fig. 12). In some of the cases in which the larger arteries were occluded, anastomotic vessels were seen traversing the pleura, and although a few of these were broncho-pulmonary communications, the majority appeared to be collateral interpulmonary channels which linked the blood supply of adjacent lobules (Fig. 13). The presence of broncho-pulmonary communications could be inferred when during injection the opaque mass flowed out of the bronchial artery into the pulmonary artery, and the communications could occasionally be demonstrated in the magnified arteriograms. The pulmonary arteriogram, therefore, has proved

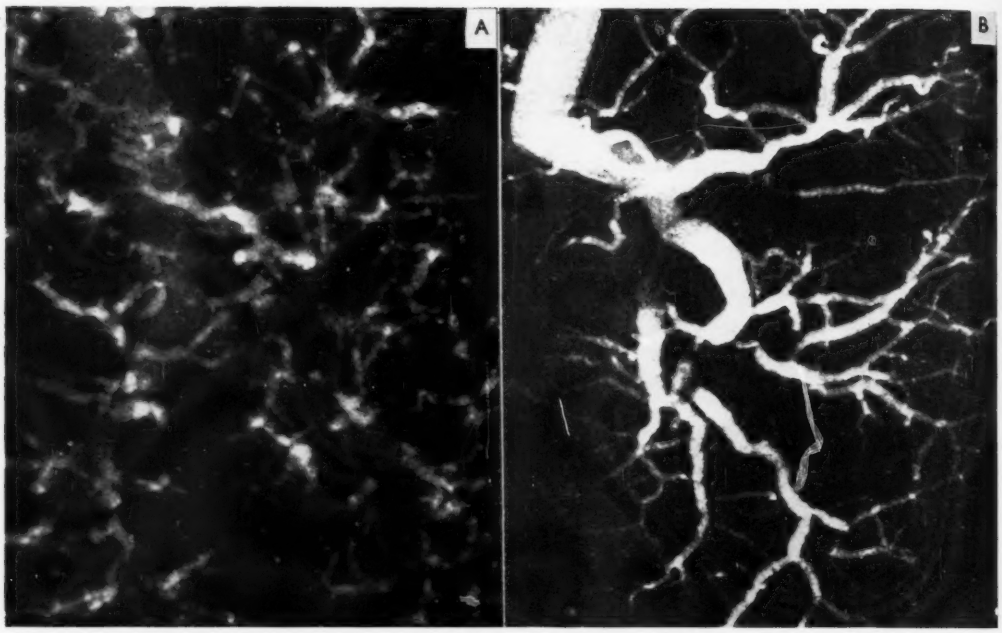

FIG. 12.—Magnified pulmonary arteriogram. (A) is from a normal lung. (B) is from Case 11, showing pruning of the terminal vessels due to narrowing.

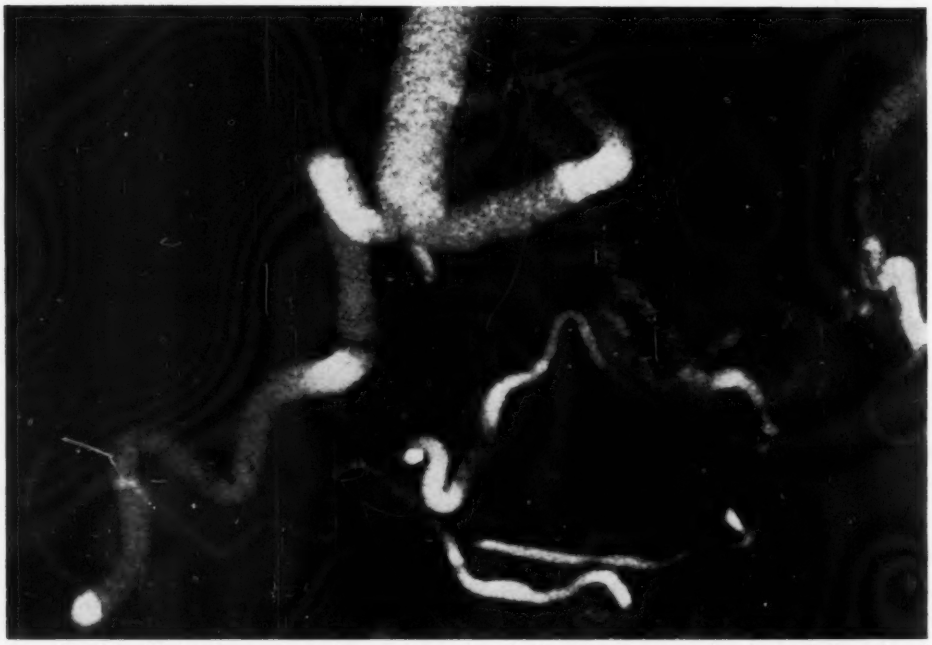

FIG. 13.—Magnified pulmonary arteriogram from Case 4. A muscular artery has been obstructed and proximal to this are a number of collateral interpulmonary channels.

itself an indispensable test in the pathological investigation of our cases. Thus, it told the extent and site of thrombosis within the larger vessels, delineating pulmonary infarcts especially when stereoscopic films were used, establishing the presence of obstruction within the muscular arteries, and even within the arterioles, indicating the place where sections should be taken for histological study, discovering the presence of abnormal arterial anastomoses, and distinguishing the arterioles from venules at subsequent microscopy.

By *histological examination* three kinds of pulmonary arteries were recognized and, following the classification given by Brenner (1935), they are designated elastic arteries, muscular arteries, and arterioles. The elastic arteries show three or more well-defined elastic coats (Fig. 14A), the muscular arteries two elastic coats separated by circular muscular fibres (Fig. 14B), and the arterioles a single elastic coat (Fig. 14C). The transition between an elastic and muscular artery takes place where the external diameter of the vessel is approximately 1·0 mm., and between a muscular artery and arteriole where the diameter is about 0·1 mm. The adventitia is not included in a measure of the diameter since it is often ill-defined. It follows that vessels referred to in this paper as muscular arteries correspond with the *artérioles musculaires* of French authors,

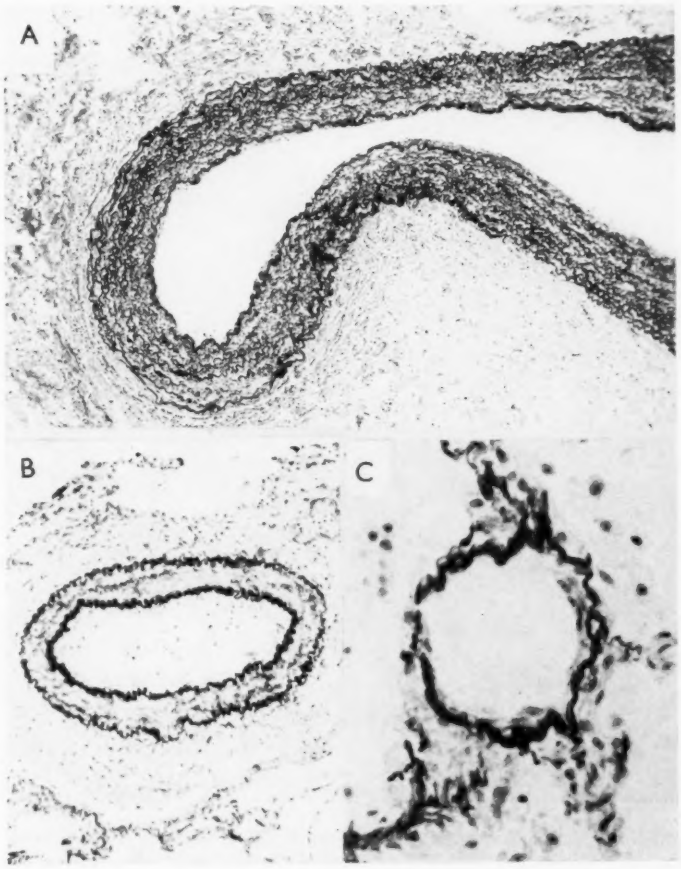

FIG. 14.—Normal pulmonary arteries. (A) Elastic artery (×50). (B) Muscular artery (×100). (C) Arteriole (×300).

and arterioles to their *pré-capillaires*. Arterioles closely resemble venules on histological examination and unless they are seen arising from a muscular artery they can only be distinguished with certainty following a pulmonary arteriogram.

Arteriography could not always distinguish the bronchial arteries from branches of the pulmonary artery as both were sometimes filled with the injected material. The histology of the bronchial arteries, however, has been carefully described by Verloop (1948), and the identification of these vessels does not as a rule present any difficulty. Thus, before penetrating the bronchial wall they have a thin muscular coat lined by a dense internal elastic membrane. In the wall of the smaller air passages the longitudinal muscle fibres of the intima of the bronchial arteries increase greatly in number so that the intima is several times thicker than the media, causing the lumen to become very narrow or even closed. In the small bronchial arteries the media may also enlarge, and at the same time its muscle fibres may change in direction and course round the lumen in spiral fashion, ultimately lying almost parallel with the longitudinal fibres of the intima (Fig. 15).

We have elected to describe the histology of lone or solitary pulmonary hypertension by reference to our own material, since in reported cases the location of the vascular changes in the pulmonary arterial tree has not always been exactly defined.

In the *elastic arteries* intimal thickening was more noticeable than in normal subjects of the same age. Thrombosis of one or two segmental arteries was a common finding, and it sometimes involved the muscular

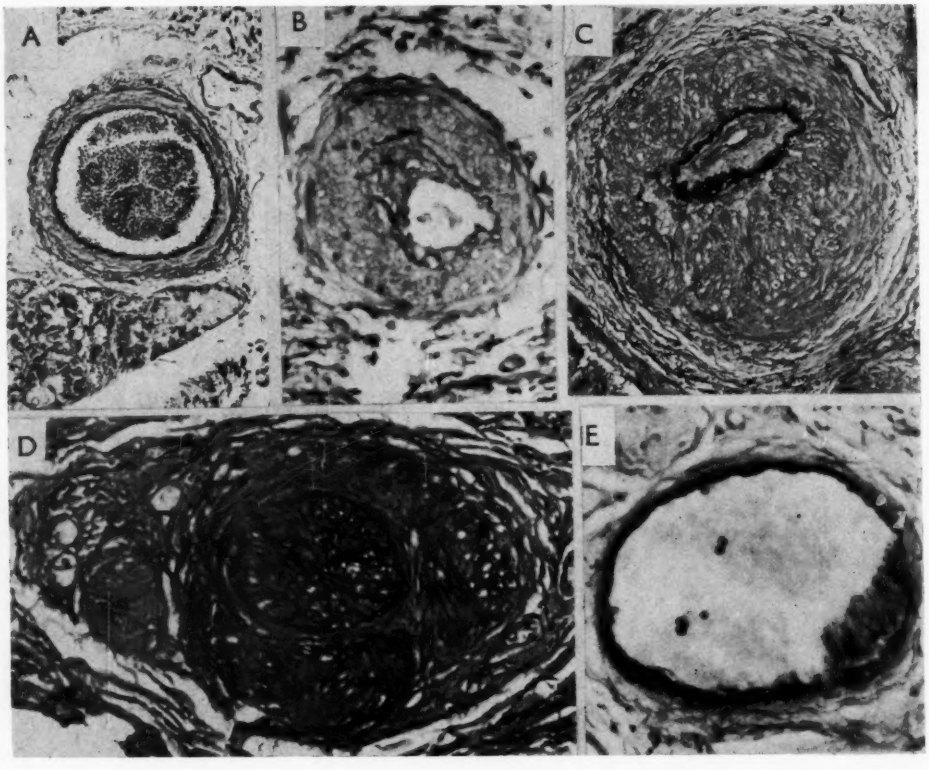

FIG. 15.—Normal bronchial arteries. (A) Free artery with thin muscular coat and dense internal elastic covering (×100). (B) and (C) Thin media and great thickening of intima causing great narrowing of the lumen (×300 and ×100 respectively). (D) Great thickening of media where its muscle fibres course in compartmental bundles. The intima is also thickened obliterating the lumen (×200). (E) Thin media with dense elastic lining and large lumen (×300).

arteries. It needs emphasizing that thrombosis is a common complication of pulmonary vascular disease whether of the solitary type or associated with mitral stenosis or congenital heart disease such as atrial septal defect. The finding of thrombosis in the larger arteries does not imply that the vascular disease is primarily embolic or thrombotic, if typical histological changes are found in the small vessels and if the arteriogram shows widespread narrowing of the peripheral pulmonary vasculature.

The most significant changes in our cases had taken place in the *muscular arteries* and arterioles. These vessels were often partially or wholly occluded by an abnormal sparsely cellular tissue, and it has been impossible to decide with certainty from histological examination whether the tissue was of thrombotic origin or the result of an intimal reaction. Harrison (1948) showed that pulmonary emboli produced experimentally in the animal may in the course of time shrink to mere plaques of intimal thickening. In the case of solitary pulmonary hypertension, however, we believe that the process is mostly reactive or reparative, even though in part thrombotic, and we have therefore styled it *intimal proliferation*.

In the muscular arteries this intimal change was related to areas of medial hypoplasia or aplasia, or very rarely focal necrosis. Medial hypoplasia did not as a rule disturb the external circular appearance of the artery because the outer elastic coat of the media, supported by the adventitia, usually remained unindented. On the other hand, the inner elastic coat approached the external coat where the media showed hypoplasia, becoming contiguous with it at sites of medial aplasia (Fig. 16 to 19). Where intimal prolifera-

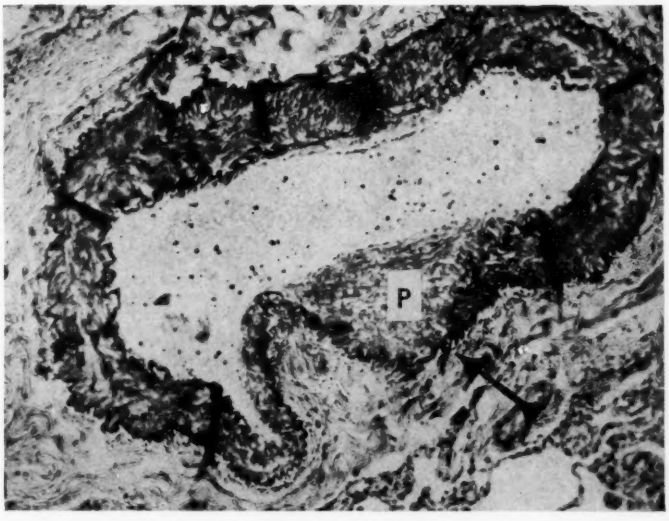

FIG. 16.—Muscular pulmonary artery (×100) from Case 6. Intimal proliferation (P) formed in bay created by aplasia of the media where the internal and external elastic coats coalesce (arrow).

tion largely occluded the artery, the media was often hypoplastic or even aplastic around its entire circumference (Fig. 20). Occasionally in such circumstances the intimal tissue was seen to bulge through the defect in the arterial wall (Fig. 21). The intimal proliferation was often greatest at the mouths of arterial branches. Medial hypertrophy has often been described in pulmonary hypertension, but it is difficult to gauge owing to the varying degree of post-mortem contraction that may be present. We were unable to identify medial hypertrophy with assurance in most of our cases.

The *arterioles* usually showed intimal proliferation whenever the muscular arteries were obstructed (Fig. 22A and B), and once (Case 9) there was partial or complete arteriolar occlusion in the absence of any intimal proliferation in the muscular arteries (Fig. 22C). We failed to find in our cases a definite muscular coat between two elastic laminæ in vessels of arteriolar size as described in pulmonary hypertension

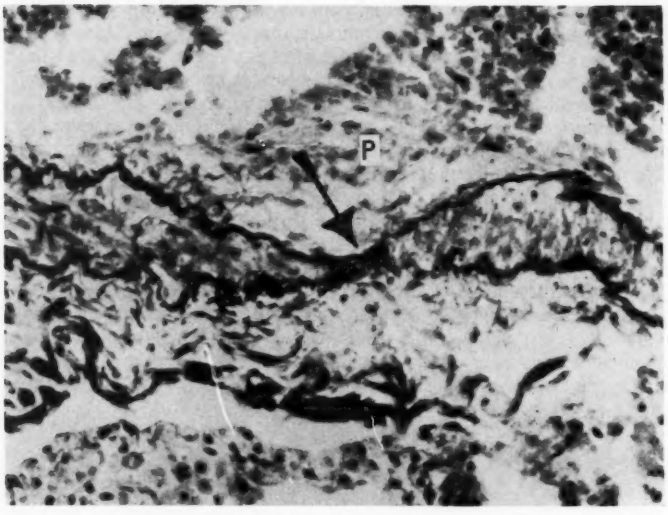

FIG. 17.—Section of muscular pulmonary artery (×300) from Case 7. Intimal proliferation (P) formed in the bay created by hypoplasia of media which has caused the internal and external elastic coats to become contiguous (arrow).

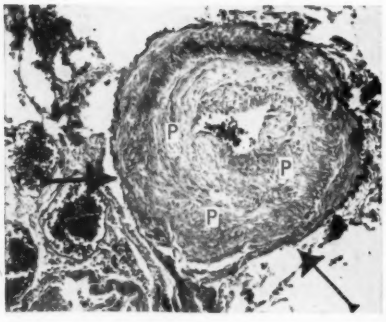

FIG. 18.—Muscular pulmonary artery (×81) from Case 3. Intimal proliferation (PPP), producing great narrowing of lumen, has specially formed in bulge caused by aplasia of the media. The two elastic coats have coalesced at the edges of this bulge (arrow).

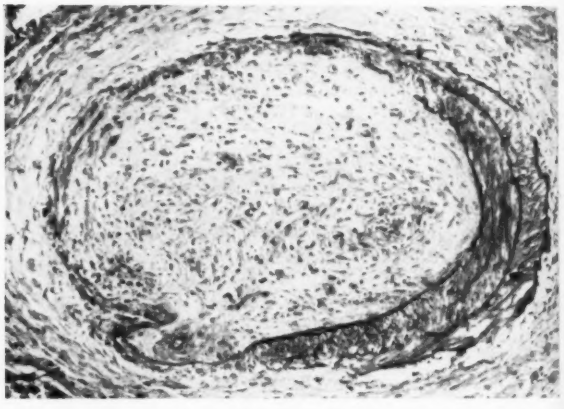

FIG. 19.—Large muscular pulmonary artery (×81) from Case 2. Intimal proliferation has obliterated the lumen. Aplasia of the media with coalescence of the elastic coats involving half its circumference.

associated with mitral stenosis and with congenital heart disease by Henry (1952) and by Heath and Whitaker (1955*a* and *b*).

In Cases 10 and 11 both the muscular arteries and the arterioles appeared normal on histological examination. An arteriogram was performed in one of these two, and showed diffuse narrowing of all the lobular arteries and arterioles to half the normal diameter (see Fig. 12B). The possibility that this appearance was

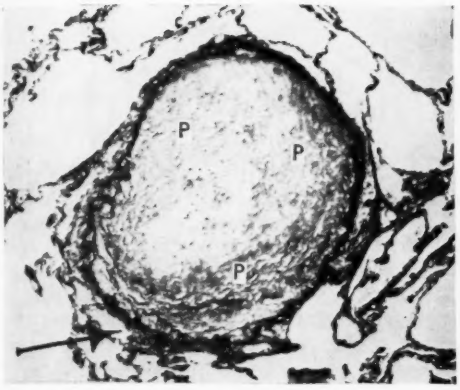

FIG. 20.—Large muscular pulmonary artery (×79) from Case 4. Intimal proliferation (PPP) has almost closed the lumen. Aplasia of media has obliterated this coat over the whole circumference of the artery except for a small remnant (arrow).

FIG. 21.—Large muscular pulmonary artery (×26) from Case 4. Intimal proliferation (PP) has caused bulging (arrows) at places where external and internal elastic coats have coalesced from medial aplasia.

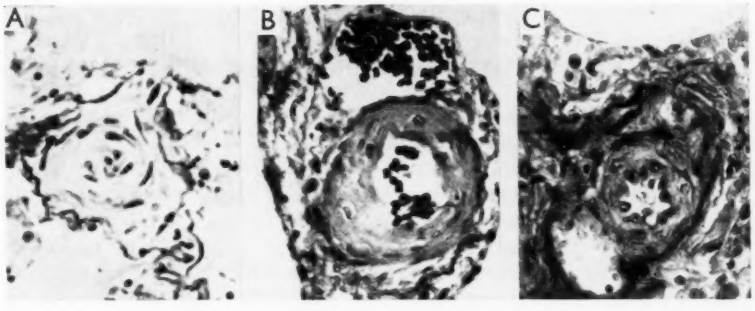

FIG. 22.—Pulmonary arteries (×300), showing intimal proliferation, wholly (A) or partially (B) occluding lumen, from Cases 5 and 3 respectively. (C) Arteriolar obstruction, with pallisading appearance, from Case 9.

an artefact has been considered by Short (1956) and ruled out on the grounds that histological examination showed the entire arterial bed to have been fully distended and normally filled. It is concluded therefore that in this case (Case 11) and in Case 10 which resembled it histologically, pulmonary hypertension was due to a persistent reduction in calibre of the pulmonary vascular bed from lack of normal distensibility.

The *venous system* was generally normal, but two cases showed subintimal thickening in the venules which was more extensive than that appearing in our normal controls (Fig. 23). An identical appearance was noted by Mallory (1937) in a case of pulmonary vascular disease.

The extra-pulmonary *bronchial arteries* were normal, but their intrapulmonary branches were often prolific, especially in the neighbourhood of obliterated muscular or elastic arteries. In several cases, the presence of broncho-pulmonary anastomosis had been demonstrated.

THE PATHOGENESIS OF SOLITARY PULMONARY HYPERTENSION

The main problem is to determine whether occlusive pulmonary vascular disease initiates hypertension, or whether hypertension based on some functional mechanism precedes and causes the

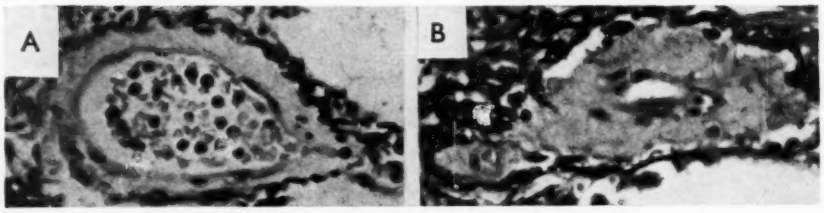

FIG. 23.—Pulmonary venules (×300). Slight intimal thickening in (A) from a normal lung, but much greater in (B) from Case 11, where it almost closes the lumen.

arterial lesions. It is often stated that in some cases pulmonary arterial disease is absent or so slight that it is insufficient to explain hypertension. In 9 of our 11 cases the degree of vascular obstruction, especially when portrayed in an arteriogram of the whole pulmonary arterial tree, was ample to account for a maintenance of hypertension. In the remaining two no histological evidence of vascular disease was found, but an arteriogram performed in one of them showed a diffuse narrowing of the smaller arteries and arterioles to half their normal calibre, suggesting that there was an inability of the arterial tree to dilate, a sort of *arterial achalasia*. Such a condition would explain pulmonary hypertension under normal increases in pulmonary flow, and this in turn might initiate intimal proliferation. Edwards (1950) has invoked a similar mechanism to explain the pulmonary vascular disease of Eisenmenger's syndrome in which he believes there is a persistence of the narrow fœtal pulmonary vasculature.

Bredt (1932), from a histological study of primary pulmonary arteriosclerosis, considered that the disease started in the media as a circumscribed loss of muscle and elastica, which was specially evident in arteries having a diameter of about 0·25 mm.; the intima showed proliferation which was slight in the larger arteries but often occluded the smaller branches. Gilmour and Evans (1946) were the first to state that congenital deficiencies in the walls of the lesser pulmonary arteries supplied the cause of pulmonary hypertension of the solitary type. In one such case they found that foci of medial aplasia or hypoplasia in the small muscular arteries numbered many thousands, and that intimal proliferation over the deficiencies led to arterial stenosis or occlusion and to persistent hypertension. The present investigation has confirmed the frequency and importance of focal medial hypoplasia or aplasia in solitary pulmonary hypertension, supporting the view that these medial defects cause an intimal reaction to normal fluctuations in pulmonary arterial pressure, and in this way initiate hypertension.

Posselt (1908) reported three examples of primary pulmonary sclerosis in infants, in two of whom syphilis in the parents was considered to be the cause of the arterial lesions, and Ljungdahl in 1915 suggested that as the effects of pulmonary sclerosis had appeared in Posselt's cases in the first months of life, the condition might be a congenital abnormality. Clarke *et al.* (1927) cited the familial occurrence of pulmonary vascular disease as evidence of its congenital origin, and a similar example of familial incidence was reported by Dresdale *et al.* (1954). We sought other congenital abnormalities in our cases and found skeletal deformities in Case 2, congenital hypoplasia of the aorta and pulmonary trunk, abnormal origin of the vertebral artery and patent foramen ovale (pencil size) in Case 9, and patent foramen ovale (probe size) in Case 7.

In 1951 Evans, from a pathological investigation which included bronchial and pulmonary arteriography, considered the mechanism that in pulmonary hypertension of the primary kind depended on the presence of congenital medial deficiencies in the lesser pulmonary arteries, also operated in pulmonary hypertension whenever it was associated with congenital dilatation of the pulmonary artery, patent ductus arteriosus, atrial septal defect, pulmonary cystic disease, or emphysema. In that such a mechanism was common to these several clinical states, Evans considered that it justified their inclusion under the title of congenital pulmonary hypertension.

The theory that intimal proliferation is of embolic or thrombotic origin is based partly on experimental evidence (Harrison, 1948; Barnard, 1954) and partly on authenticated cases of pulmonary hypertension associated with recurrent embolism (Castleman and Bland, 1946). Admitting that the histological distinction between intimal proliferation and organized thrombosis may be difficult, we still believe it is unlikely that embolism can explain many cases of isolated pulmonary hypertension, especially when it occurs in young subjects.

Brinton (1950) and Froment *et al.* (1954) have suggested that abnormal broncho-pulmonary anastomoses may cause pulmonary hypertension. There is indeed evidence that such a communication raises the pulmonary arterial pressure. Thus, Liebow *et al.* (1950) catheterized the pulmonary arteries in a patient with regional bronchiectasis, and found both the pressure and the oxygen saturation higher in the artery feeding the diseased part than in the branches supplying healthy portions of the lungs. In our cases, however, although abnormal broncho-pulmonary anastomoses were demonstrated, the extra-pulmonary bronchial arteries were not enlarged. It seems unlikely, therefore, that these vessels could carry sufficient blood to double the flow through the pulmonary arterioles, and even then the effect would be no greater than that of a moderate patent ductus arteriosus.

Summary and Conclusions

Solitary pulmonary hypertension is defined as a persistent elevation of pulmonary arterial pressure sufficient to produce enlargement and ultimately failure of the right ventricle, where the cause is confined to obstruction in the lesser pulmonary arteries of intrinsic origin. We have described 11 cases, each investigated clinically and at necropsy.

The condition is far commoner in women than in men and all our cases happened to be female. Our youngest patient died at the age of 7, the oldest at 64; the remaining nine survived to ages of between 20 and 40 years.

The dominant symptom was rapidly increasing dyspnœa on exertion which usually culminated in paroxysmal dyspnœa and orthopnœa. Cyanosis was absent or slight at the start but sometimes became intense later on when heart failure had set in. Finger clubbing was absent in all but one. Cardiac pain, always accompanied by dyspnœa, was present in 6 cases, and syncope in 5; both symptoms occurred either during effort or paroxysms of dyspnœa, and were attributed to a low cardiac output.

The pulse was small or became so, and the blood pressure a little low. The jugular venous pulse showed an exaggerated auricular wave in 6 cases. Palpation gave evidence of right ventricular hypertrophy as a rule. Auscultation at the pulmonary area usually showed an early systolic ejection sound, often a murmur maximal in mid-systole, a loud and closely split second sound, and in 4 cases a diastolic murmur of pulmonary incompetence. A triple rhythm at the apex was common late in the illness. Slight or moderate polycythæmia was found in 8, sometimes with leucocytosis. The Wassermann reaction was always negative. Slight arterial anoxæmia was the rule.

Radiological findings included enlargement of the right atrium and ventricle, and dilatation of the pulmonary trunk. The main pulmonary branches were almost always enlarged, but the peripheral lung fields appeared ischæmic, and plethora was never seen. The electrocardiogram proved an indispensable test, always exhibiting the pattern of right ventricular hypertrophy especially in leads CR1 or V1, and usually with evidence of right atrial hypertrophy.

Cardiac catheterization, performed in 7 cases, excluded an intracardiac shunt and always showed considerable elevation of pulmonary arterial and right ventricular pressure.

The clinical course was inexorably downhill, the average duration of life from the onset of cardiac symptoms being $2\frac{1}{2}$ years; this was less in the younger than in the older patients.

In diagnosis, chronic lung disease, mitral stenosis, and congenital heart disease had to be excluded. The distinction between solitary pulmonary hypertension and that resulting from recurrent pulmonary embolism sometimes proved impossible during life, and difficult even at necropsy.

Pathological examination always showed hypertrophy of the right ventricle with dilatation of the pulmonary trunk and usually of its main branches. Thrombotic occlusion of one or more of the segmental branches was common. The *pulmonary arteriogram* portrayed the site and extent of arterial occlusion and the presence of abnormal arterial anastomoses, thus providing a valuable guide for histological examination.

The most significant histological changes were found in the muscular arteries and arterioles. These were partly or wholly occluded by intimal proliferation in which thrombosis with subsequent organization may have played a part. In the muscular arteries, the intimal changes were related to areas of hypoplasia or aplasia in the media. In nine cases, the vascular obstruction accounted for a maintenance of pulmonary hypertension. In the remaining two, no such obstruction was found on histological examination, but an arteriogram carried out in one of them showed a generalized constriction of the lesser pulmonary arteries, implying that a narrowed pulmonary vasculature (arterial achalasia) predisposed to the pulmonary hypertension.

Many colleagues have given invaluable aid in the clinical and pathological investigation of our 11 cases, which it is a pleasure to acknowledge. Thus, Cases 5, 8, and 11 were under the care of Dr. Frederic Jackson and Case 11 was referred to him by Dr. F. O. Graham, while Dr. B. E. Tomlinson examined them at necropsy. Case 2 was under the care of Dr. Paul Wood, Case 4 under Dr. W. Somerville, Case 9 under Dr. Wallace Brigden, Case 10 under Dr. J. H. L. Easton, and Case 7 under Dr. W. G. Wyllie. Dr. R. Hudson contributed to the pathological study of Cases 2 and 3 and gave valuable assistance throughout the investigation. Dr. M. Bodian helped with Case 7, and Dr. J. Valentine with Case 10. Professor Dorothy Russell and Dr. D. J. O'Brien gave us advice about Cases 1, 2, 5, 8, 9, and 11. Dr. J. Shillingford carried out the pulmonary arteriograms in the earlier cases. We wish to thank these several colleagues for help which each so readily gave us.

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Case Notes

Glossary of Abbreviations. MSL=Midsternal line. MCL=Midclavicular line. LA=Left atrium. LV=Left ventricle. RA=Right atrium. RV=Right ventricle. SVC=Superior vena cava. PA=Pulmonary artery. RUL and RLL=Right upper and lower lobes. LUL and LLL=Left upper and lower lobes. BP=Blood pressure in mm. of Hg. PCP=Pulmonary capillary pressure. RBC=Red blood cells in millions per c.mm. WBC=White blood cells per c.mm. Hb=Hæmoglobin expressed as percentage. WR=Wassermann reaction. Wt.=Weight of heart. FOC=Foramen ovale closed. EC=Electrocardiogram.

Case 1. A. D., married woman, aged 36, seen in 1952, had been well until a breathless attack ten months before, after which she became breathless on slight exertion and had occasional hæmoptysis. Dyspnœa was soon joined by chest pain and tightness in the throat on effort, confining her to bed. Following attacks of nocturnal dyspnœa with constriction in the chest, she was admitted to hospital.

Examination. Cyanosed and orthopnœic; no finger clubbing. Pulse small and regular. BP 170/130 falling to an average level of 120/95. Large *a* waves in jugular pulse. Apex beat in MCL, systolic lift over conus. Mitral systolic murmur and triple rhythm due to the third sound or opening snap; split second sound with very loud pulmonary element. Liver palpable, slight œdema of ankles, lungs clear. RBC 8·88, Hb 140, WBC 18,900. WR negative.

Radiology. Moderate enlargement of RV and RA, pulmonary trunk and main branches. Peripheral lung fields ischæmic. Scar of infarct in RLL.

EC. Normal rhythm, RV hypertrophy.

Cardiac catheterization excluded an intracardiac shunt.

Course. She improved in hospital but after discharge was soon incapacitated by dyspnœa, chest pain on effort, recurrent hæmoptysis, and later she had repeated syncope while standing. Following attacks of nocturnal dyspnœa, she was readmitted to hospital in congestive failure with ascites. Pulse very small; BP 110/70. Auscultation showed a pulmonary diastolic murmur, a louder mitral systolic murmur, and the third heart sound or opening snap. Treatment was ineffective. Though the pulmonary hypertension was regarded as solitary, mitral stenosis could not be entirely excluded in view of the clinical signs, so that exploratory cardiotomy was performed and mitral disease excluded. PA pressure 70/40 mm. She became drowsy and died 2½ years after the onset of symptoms.

Necropsy. Very wasted cadaver. Customary signs of heart failure in viscera. No thrombosis of pelvic or femoral veins.

Heart. Wt. 330 g. Dilatation and moderate hypertrophy of RV (0·7 cm. thick). Considerable dilatation of RA. Coronary arteries and valves normal. FOC. No congenital defects. Adherent thrombi in right auricular appendage and in RV.

Lungs. Massive thrombus, much of it old, in both pulmonary arteries, with complete occlusion of the main artery to the RLL. No emphysema.

Arteriogram (Fig. 9) showed no enlargement of PA or its primary branches, but there were a number of large filling defects due to occlusion of the pulmonary arteries as well as areas of opaque material indicating infarcts. Peripheral vessels where filled were natural. Normal bronchial artery filled with opaque medium.

Microscopy. Many elastic arteries occluded or greatly narrowed by organizing thrombus. Some muscular arteries healthy, others greatly obstructed by granulation tissue or intimal proliferation often associated with medial aplasia. Many arterioles similarly occluded and occasionally contrasted to show pallisading appearance. Bronchial arteries numerous.

Case 2. M. T., married woman, aged 24, seen in 1952, had a cardiac murmur at age of 18 months. When 15, she fainted while running for a bus, and at this time was treated for rheumatism, after which she first noticed dyspnœa on exertion. When 23, she was in hospital with pyrexia and pain in right iliac fossa; bacterial endocarditis was suspected and penicillin given; blood culture was negative. Thereafter, increasing breathlessness and fatigue on exertion set in. Some months later, attacks of nocturnal dyspnœa and a dry cough developed. Admitted to hospital with abdominal pain, nausea, and vomiting.

Examination. No cyanosis or clubbing of fingers. Pulse small and regular. BP 100/80. Large *a* wave in jugular pulse. Apex beat 9 cm. from MSL, of right ventricular type. Moderate systolic lift over RV. A sound in early systole, closely split second sound with loud pulmonary element, and early diastolic murmur heard in pulmonary area. No signs of heart failure. RBC 6·01, Hb 120, WBC 17,950. WR and Kahn negative.

Radiology. Considerable enlargement of RV and RA. Pulmonary trunk and both main branches grossly dilated. Peripheral lung fields ischæmic.

EC. Normal rhythm, RV hypertrophy, large P waves.

Cardiac catheterization. PA mean pressure 63 mm. Hg. Oxygen saturation femoral artery, 93 per cent.

Course. In spite of rest and treatment, œdema of ankles spread to the trunk; pulse became impalpable, extremities cold, and dyspnœa increased. Right-sided pleurisy accompanied the onset of pulmonary infarction. After improving for a time, she became cyanosed, drowsy and breathless, the pulse rose to 150, she complained of retrosternal discomfort, and died 6 weeks after admission and about 15 months from the onset of her main symptoms.

Necropsy. Customary signs of heart failure in viscera. No thrombosis of systemic veins.

Heart. Wt. 480 g. Considerable enlargement of RV (0·9 cm. thick). LA and LV (1·2 cm. thick) normal. RA slightly dilated. Coronary arteries and valves normal. FOC. No congenital defects or cardiac thrombosis.

Lungs. PA 8·8 cm. circumference (aorta, 6·0 cm.) and both branches greatly dilated, with minimal atheroma. Artery to RLL narrowed by thrombus near origin. Artery (0·2 cm. diam.) in RUL occluded by thrombus. No emphysema.

Microscopy. Elastic arteries showed only patchy intimal thickening. Muscular arteries showed hypoplasia and aplasia of media, their inner and outer coats coalescing (Fig. 19). Great intimal proliferation adjoining such deficiencies, partially or wholly occluding artery, and in places herniating through attenuated wall. Others showed focal necrosis with local bulging and overlying deposit of thrombus. Many vessels (0·25 mm. diam.) with normal intima, seemed thickened. Arterioles showed intimal proliferation. Bronchial arteries were natural.

Case 3. E. B. C., married woman, aged 62, was seen in March 1948. For 5 years she had been subject to constricting pain behind upper sternum, sometimes extending to both arms, on exertion and always associated with dyspnœa. In a severe attack of chest pain she had fainted and coronary thrombosis was suspected. Increasing dyspnœa on effort followed.

Examination. No cyanosis or clubbing of fingers. BP 140/85. Apex beat slightly displaced to left. No murmurs. Pulmonary second sound very loud and split. RBC 5·1, Hb 100, WR negative.

Radiology. Moderate enlargement of RA and RV; pulmonary trunk prominent, both main branches enlarged and pulsatile.

EC. Normal rhythm, RV hypertrophy, large P waves in lead II.

Cardiac catheterization. RV mean pressure 47 mm. Hg. Arterial oxygen saturation 84 per cent.

Course. She developed cough and hæmoptysis and was admitted to hospital in May 1949 in heart failure with cyanosis, cold extremities, and small pulse. Later she had four syncopal attacks, and died of heart failure 7 years after the onset of cardiac pain, and less than three years after her first symptoms of heart failure.

Necropsy. Customary signs of heart failure in viscera. No thrombosis of pelvic or femoral veins.

Heart. Great hypertrophy of RV (1·3 cm. thick). LV normal (1·1 cm. thick). Coronary arteries and valves normal. FOC. No congenital defects or cardiac thrombosis.

Lungs. No infarction or emphysema. Considerable dilatation of PA (2·2 cm. diam. compared with 1·8 cm. for the aorta).

Microscopy. One or two elastic arteries occluded by thrombus. Hypoplasia and sometimes aplasia of many muscular arteries causing external and internal elastic layers to coalesce. Adjacent to these areas and elsewhere, conspicuous intimal proliferation caused severe narrowing or occlusion of the affected arteries (Fig. 18). Some *arterioles* appeared healthy, but many showed intimal proliferation which sometimes occluded these vessels (Fig. 22B). Many collateral vascular channels seen. Bronchial arteries prolific, especially near obstructed muscular arteries.

Case 4. P. M., a single woman, aged 21, seen in May 1955, had suffered from epilepsy since the age of 18, but otherwise had remained well and free from symptoms until 10 months ago, when she had bronchitis and thereafter became breathless and cyanosed on exertion, so that she could only walk 25 yards without halting. For a month, cramp-like pain in left chest on effort was relieved by halting, and there were two short attacks of nocturnal dyspnœa with constriction in the throat and cough.

Examination. Pulse small and regular. BP 105/75. Jugular pulse showed giant *a* waves. Apex beat of right ventricular type. Triple rhythm. Very loud split second sound in pulmonary area. No murmurs.

Liver palpable. No œdema. A short walk provoked intense dyspnœa and cyanosis of lips and extremities. Hb 106, WBC 7,900. WR negative.

Radiology. RA prominent. Pulmonary trunk grossly dilated, main branches slightly enlarged, and peripheral lung fields ischæmic.

EC. Normal rhythm, RV hypertrophy, large P waves in leads II and III.

Cardiac catheterization. PA pressure 118/80 mm. Hg. Arterial oxygen saturation: femoral artery, 70 per cent.

Course. Following a major epileptic fit, she became severely breathless and distressed, and died suddenly less than a year from the onset of symptoms.

Necropsy. Customary changes of heart failure in viscera. No thrombosis in pelvic or femoral veins.

Heart. Wt. 425 g. Great hypertrophy of RV (1·2 cm. thick) (LV 0·9 cm. thick). Hypertrophy and dilatation of RA. Coronary arteries and valves healthy. No congenital defects or cardiac thrombosis.

Lungs. Three small infarcts, but no evident thrombosis. Slight emphysema in LUL. PA dilated (3·6 cm. diam.) (aorta 2·0 cm. diam.). Right *arteriogram* showed severe pruning of peripheral vascular pattern and moderate bronchial reflux (Fig. 11 and 13).

Microscopy. Non-occlusive thrombosis, of different ages, of large elastic arteries. Organizing thrombus often filling branches of muscular arteries at their origin. Many arteries partly or wholly filled with intimal proliferation showed medial hypoplasia or aplasia (Fig. 20 and 21). Many arterioles occluded, others merely ghosts. Undilated bronchial arteries prolific.

Case 5. N. V. R., a married woman, aged 24, was first seen in November 1951 when she was 5 months pregnant. Slight breathlessness for 2 years, worse since bronchitis a year ago. Dyspnœa had increased during pregnancy and a dry cough developed, but she had remained at work until admitted to hospital.

Examination. Pulse regular, 100. BP 105/75. Very loud pulmonary second sound. Triple rhythm at apex. Liver enlarged, œdema of ankles, and raised jugular venous pressure.

Radiology. Heart slightly enlarged with RA prominent. Pulmonary trunk and right main branch much enlarged, medium branches normal or narrowed, peripheral lung fields ischæmic.

EC. Normal rhythm, RV hypertrophy.

Course. Admitted to hospital for termination of pregnancy by hysterotomy. She died suddenly 4 days later and about 2 years after the onset of symptoms.

Necropsy. Customary signs of heart failure in viscera. No thrombosis of systemic veins.

Heart. Wt. 250 g. Great dilatation of RV. Coronary arteries and valves normal. No congenital defects or cardiac thrombosis.

Lungs. No infarction or emphysema. Right pulmonary *arteriogram* showed great distension of right PA. Medium arteries appeared to be normal, but lesser ones were pruned.

Microscopy. Apart from a single elastic artery which was occluded by thrombus all vessels of a diameter greater than 0·2 mm. were healthy. The small muscular arteries showed aplasia and hypoplasia of the media, and great intimal proliferation which often occluded the vessels. Similar intimal proliferation had closed many arterioles (Fig. 22A).

Case 6. M. A., a married Englishwoman, aged 33, with one child, was seen in November 1951. She had resided in India and E. Africa for several years, had been in good health until she became breathless when playing tennis, and thereafter noticed increasing dyspnœa accompanied by tightness in the chest on effort. Within 3 months, attacks of severe griping central chest pain apart from effort set in, followed by epigastric oppression, vomiting and abdominal distension, and by nocturnal dyspnœa, orthopnœa, and attacks of faintness on effort.

Examination. No cyanosis or clubbing of fingers. Pulse small and often impalpable. BP 95/70. Apex beat in MCL. No murmurs. Second sound in pulmonary area loud and split. Jugular veins distended and showing dominant *a* waves. RBC 6·0, Hb 135, WBC 9,350. Arterial oxygen saturation 89 per cent. WR and Kahn negative. Urine and stools negative for bilharzia ova.

Radiology. Moderate enlargement of RA, RV, pulmonary trunk and main branches; peripheral lung fields ischæmic.

EC. Normal rhythm, RV hypertrophy.

Cardiac catheterization. PA pressure 67/25 mm. Oxygen saturation: femoral artery 92 per cent. No evidence of intracardiac shunt.

Course. A diagnosis of solitary pulmonary hypertension was made. She improved on routine

treatment for heart failure, but on leaving hospital she deteriorated quickly and was readmitted. Examination then showed a pulmonary systolic click, a pulmonary diastolic murmur, triple rhythm, and signs of tricuspid incompetence. She developed increasing weakness, apathy, cyanosis with cold extremities, and finally repeated syncopal attacks without convulsions. She died 2½ years after the onset of symptoms.

Necropsy. Customary signs of heart failure in viscera. No thrombosis in pelvic or femoral veins.

Heart. Wt. 330 g. Dilatation and hypertrophy of RA and RV (1·0 cm. thick as also was LV). Coronary arteries and valves healthy. FOC. No congenital defects or cardiac thrombosis.

Lungs. No infarction or emphysema. PA thin and slightly dilated, showing some atheroma. Thrombus in lesser arteries to RUL and RLL.

Microscopy. Prominent intimal proliferation in large elastic arteries. Similar intimal proliferation occasionally seen in large muscular arteries overlying areas of medial hypoplasia (Fig. 16). The main abnormalities found in vessels less than 0·15 mm. diameter. Many of these showed medial aplasia with adjacent intimal proliferation causing severe narrowing and often complete occlusion. Similar occlusion in numerous arterioles. Collateral vascular channels evident. The bronchial arteries appeared normal.

Case 7. T. B., a girl, aged 7, admitted to hospital in March 1946, had been healthy and active until three months before when she became easily tired and breathless on effort.

Examination. Cyanosis. No clubbing of fingers. Pulse small, regular and 120. Orthopnœa. Apex beat 3·7 cm. outside MCL. Mitral systolic murmur, splitting of second sound in the pulmonary area. Jugular veins distended and signs of tricuspid incompetence. Liver enlarged and œdema present.

Radiology. Great cardiac enlargement, mainly of RA and RV. Pulmonary trunk dilated, main branches normal, and peripheral lung fields ischæmic.

EC. Normal rhythm, RV hypertrophy, large P waves in lead II.

Course. Heart failure increased in spite of treatment. She collapsed and died suddenly 5 months after the onset of symptoms.

Necropsy. Customary signs of heart failure in viscera. No thrombosis in pelvic or femoral veins.

Heart. RV enlarged (RV 7 mm. thick; LV 11 mm. thick). Coronary arteries and valves normal. Foramen ovale patent to probe. Ductus arteriosus closed. Thrombus, size of walnut in RA.

Lungs. Thrombus blocking both main pulmonary arteries (Fig. 8). Two wedge-shaped infarcts in right lower lobe. No emphysema.

Microscopy. Elastic arteries showed widespread thrombosis often with recanalization. Similar changes or intimal proliferation in muscular arteries accompanying medial hypoplasia (Fig. 17) and also in arterioles, which were often occluded. Bronchial arteries prolific near thrombosed elastic arteries. Collateral vascular channels throughout lung.

Case 8. A. G., a married woman, aged 37, with two children had rheumatic fever at age of 21, when her heart was suspected. Well until a year before, when she became breathless on effort; dyspnœa had increased in recent months when she became orthopnœic at night, and noticed upper chest pain after a busy day. Admitted to hospital in 1951.

Examination. Moderate cyanosis. Pulse small, regular, 136. BP 140/80. Jugular veins engorged. A moderate systolic murmur and loud second sound at pulmonary area. Liver enlarged. Slight œdema of ankles and sacrum. Hb 120. WBC 17,000.

Radiology. RV and RA moderately enlarged. Pulmonary trunk prominent, main branches enlarged and peripheral lung fields of normal clarity.

EC. Normal rhythm, RV hypertrophy, large P waves.

Cardiac catheterization. PA mean pressure 74 mm. Hg. PCP 4 mm. Hg. Oxygen saturation: femoral artery, 89 per cent.

Course. Three weeks after leaving hospital she was readmitted on account of a sudden attack of left-sided chest pain and coughing with slight dyspnœa. Severe dyspnœa and deep cyanosis developed and she died half an hour later, one year after the onset of symptoms.

Necropsy. Customary signs of heart failure in viscera. No thrombosis of pelvic or femoral veins.

Heart. Wt. 400 g. Hypertrophy of RV. Coronary arteries and valves normal. No congenital defects or cardiac thrombosis.

Lungs. Few atheromatous plaques in main PA branches. No infarction or emphysema. Left *arteriogram* showed enlargement of main branch with narrowing of the medium and the finest branches.

Microscopy. Elastic arteries normal. Slight intimal proliferation within medium-sized muscular arteries. Greater proliferation, often containing conspicuous elastic tissue adjacent to areas of medial hypoplasia produced moderate narrowing of the smallest arteries. Some arterioles were partially obstructed by intimal proliferation. Moderate obstruction of venules by endothelial thickening. Bronchial arteries normal.

Case 9. V. R., a married woman, aged 27, was admitted to hospital in 1951 when three months pregnant. At age of 11, she was forbidden games on account of a heart murmur. When 16, syncopal attacks on exertion began and subsequently became more frequent. She had been slightly short-winded from the age of 16, and at age of 26 dyspnœa became so severe that she could only walk 200 yards, and she had a choking sensation in the throat on effort which lasted half an hour. She also had several attacks of nocturnal dyspnœa with tightness in the throat, palpitation, and brief syncope.

Examination. No cyanosis or clubbing of fingers. Pulse 80, small and regular. BP 110/65. Apex-beat 10 cm. from MSL and diffuse. Systolic lift over RV. Pulmonary diastolic thrill. Loud widespread systolic murmur, best heard at apex; pulmonary diastolic murmur obliterating the second sound. Liver palpable. No œdema. Lungs clear. Hb 95. WR negative.

Radiology. Gross enlargement of RV and RA; pulmonary trunk of aneurysmal size, main branches much enlarged, peripheral lung fields ischæmic. Small aorta.

EC. Normal rhythm, RV hypertrophy, normal P waves.

Course. Pregnancy was allowed to continue and she left hospital, but was soon readmitted with attacks of nocturnal dyspnœa, palpitation, and constricting central chest pain extending to both arms. She died in 12 hours, following a syncopal attack with slight convulsions, one year after the onset of unequivocal cardiac symptoms.

Necropsy. Customary changes of heart failure in the viscera. No thrombosis of pelvic or femoral veins.

Heart. Wt. 524 g. Dilatation of RA. Very great dilatation and hypertrophy of RV (1·5 cm. thick). Dilatation without obvious hypertrophy of LV (1·0 cm. thick). Coronary arteries and valves normal. Aorta was hypoplastic (0·1 cm. thick and 2·8 cm. circumference). Valvular patency of foramen ovale (1·3 cm. diameter). Left vertebral artery arising from arch of aorta.

Lungs. No emphysema. Several small granulomatous foci. Great dilatation of PA forming fusiform swelling (7·0 cm. by 4·5 cm.); both branches also greatly dilated. Fragment of organizing thrombus in artery to RUL, but without infarction here or elsewhere. *Arteriogram* showed dilatation of PA and its primary and secondary branches with pruning of terminal radicles.

Microscopy. Flecks of atheroma in elastic arteries. Muscular arteries appeared normal. Widespread obstruction of arterioles with pallisading appearance (Fig. 22C).

Case 10. J. B., a single woman, aged 31, seen in 1949, was healthy until two years before when she became breathless playing hockey, and noticed cyanosis of face and hands at times.

Examination. Slight cyanosis; curved nails. BP 110/70. Apex-beat 12 cm. from MSL. Palpable pulmonary diastolic shock. Pulmonary systolic murmur and very loud second sound. Kahn negative. Hb 118.

Radiology. Considerable enlargement of RA and RV, prominent pulmonary trunk and main branches. Peripheral lung fields normal.

EC. Normal rhythm, RV hypertrophy, large P waves in lead II.

Course. Symptoms hardly changed during next year, after which she developed a cough, became orthopnœic, and was admitted to hospital. Examination showed increased skin pigmentation, cyanosis and slight clubbing of fingers, orthopnœa, and râles over both lungs. A triple rhythm was audible. Venous pressure raised and liver enlarged. She died suddenly 3 years from the onset of symptoms.

Necropsy. Customary changes of heart failure in viscera with right pleural (500 ml.) and pericardial (200 ml.) effusion. No thrombosis of systemic veins.

Heart. Greatly enlarged. Great hypertrophy of RV (0·9 cm.); slight dilatation and hypertrophy of RA. LA and LV (1·4 cm.) normal. Coronary arteries and valves normal. FOC. No congenital defects or thrombosis.

Lungs. No emphysema, thrombosis or infarction. Pulmonary artery trunk and main branches greatly dilated, with very slight atheroma.

Microscopy. Elastic arteries, muscular arteries and arterioles were patent and appeared normal in structure. Venules normal. Bronchial arteries more numerous than usual.

Case 11. L. J., a married woman, aged 39, with two children, 1954, had experienced recurrent bronchitis for ten years. Dyspnœa and orthopnœa had been present for two years. She had been in another hospital with heart failure for several months.

Examination. Cyanosis. Pulse 80 regular. Giant *a* waves in jugular pulse. BP 160/100 falling to 135/95. Right ventricular systolic lift. Very loud pulmonary second sound. Triple rhythm due to the third heart sound. Scattered rhonchi in chest. Hb 120. WBC 13,900.

Radiology. Considerable enlargement of RV and RA; pulmonary trunk and main branches much dilated with normal peripheral lung fields.

EC. Normal rhythm, RV hypertrophy, large P waves.

Cardiac catheterization. PA mean pressure exceeded 107 mm. Hg. PCP 5 mm. Hg. Oxygen saturation: femoral artery, 63 per cent rising to 95 per cent after breathing oxygen.

Course. She developed acute pulmonary œdema and died two years after initial significant symptoms.

Necropsy. Customary changes of heart failure in viscera. No thrombosis of pelvic or femoral veins.

Heart. Wt. 400 g. Great dilatation and hypertrophy of RA and RV (1·0 cm. thick). Coronary arteries and valves normal. No congenital defects or cardiac thrombosis.

Lungs. Small bullæ, on surface, but no substantial emphysema. No pulmonary infarction. Scattered small foci of sarcoidosis, mostly in lymph glands, but a few in lungs. PA dilated and showing patchy atheroma. *Arteriogram* (Fig. 12) showed generalized narrowing of finest vessels.

Microscopy. Elastic arteries, muscular arteries and arterioles appeared normal in structure. Venules frequently showed endothelial thickening which caused considerable reduction in size of lumen (Fig. 23B). Bronchial arteries prolific.

TOTAL AND PERIPHERAL BLOOD FLOW IN ACUTE MYOCARDIAL INFARCTION

BY

G. de J. LEE

From the Department of Medicine, St. Thomas's Hospital Medical School

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Acute cardiac infarction is an event that might be expected to produce sudden left ventricular heart failure. Although circulatory collapse is common when myocardial infarction is extensive, the clinical signs of cardiac failure are not often dramatic. Recently, therapy involving intra-arterial or intravenous transfusion of patients with severe shock from myocardial infarction has been used (Epstein and Relman, 1949; Silber *et al.*, 1951; Berman and Akman, 1952; Gootnick and Knox, 1953). Similar treatment of patients with acute left ventricular heart failure would be considered foolhardy. The present study of circulatory events occurring in a group of patients admitted to hospital with acute myocardial infarction was an attempt to investigate these apparent discrepancies.

Material and Methods

Eleven patients were studied. All gave a typical history of cardiac infarction occurring within a few hours of admission, and all had electrocardiographic evidence confirming myocardial infarction. On admission, eight of the patients had antero-posterior chest tele-radiograms taken as they lay recumbent upon a stretcher in the casualty department. In six patients these X-rays were subsequently compared with similar films taken after recovery. On admission to the ward, all the patients received 1/4 gr. morphine HCl intramuscularly. Half an hour later the skin of the antecubital fossa was anæsthetized with 2 per cent xylocaine, and a 1/2 mm. polythene catheter inserted through a needle into the antecubital vein; the tip of the catheter was advanced to the superior vena cava and the mean pressure in this region measured, using a saline manometer. At the same time a second needle was inserted into the brachial artery and the blood pressure recorded using a Hansen capacitance manometer (1949). Pressures were measured with reference to the sternal angle. Cardiac output was measured using the Hamilton dye technique, a known volume of dye T1824 being injected via the venous catheter, while rapid small arterial samples were being collected simultaneously (Kopelman and Lee, 1951). The " intrathoracic blood volume " was calculated from the estimated cardiac output and mean dye circulation time. Forearm blood flow was obtained using a venous occlusion plethysmograph filled with water at a temperature of 34° C.

Two patients subsequently died: one 14 days after admission, from a secondary coronary thrombosis, and one 9 days after admission, from ventricular fibrillation. The remaining nine readily consented to repeat studies being made following recovery some 4–9 weeks after admission. Seven patients, including the two who died, had additional studies performed 1–13 days after admission.

The cardiac output and " intrathoracic blood volume " was compared with similar estimations obtained from a group of normal subjects, a group of patients with left ventricular heart failure, and a third group of patients who had recovered from left ventricular heart failure, studied previously with Dr. H. Kopelman (1951).

Results

Clinical Findings. The age of the patients varied from 44 to 64 years. Nine were men and two women.

The clinical findings on admission are shown in Table I and were arbitrarily classified in units: 0 indicated no disability other than pain, while 4 represented severe clinical " shock " manifest by prostration, stupor, a cold sweaty cyanosed skin, and a reduced or imperceptible blood pressure when measured by auscultation.

TABLE I

CLINICAL STATE OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION ON ADMISSION TO HOSPITAL

Patient	Age	Sex	" Shock " 0–4	Mental state	Pain 0–4	Skin		Sweat 0–4	J.V.P.	Lung creps. 0–4
						Temp.	Colour			
L. N.	47	F	0	Anxious	3	Warm	Pink	2	Raised	0
J. E.	61	M	0	Alert	2	Warm	Pink	0	Raised	0
W. J.	48	M	1	Dull	3	Cool	Pale	2	Not visible	0
G. C.	45	M	1	Anxious	3	Cool	Pale	2	Raised	0
R. F.	45	M	2	Dull	2	Cool	Grey	2	Raised	1
C. L.	44	M	2	Anxious	3	Warm	Pale	0	Raised	0
H. W.	59	M	3	Dull	2	Cold	Grey	2	Raised	1
W. E.	64	M	3	Dull	2	Cool	Grey	3	Raised	1
W. B.	45	M	3	Dull	1	Cold	Grey	3	Raised	0
*W. H.	64	M	3	Dull	2	Cold	Grey	2	Raised	1
*M. T.	57	F	4	Semi-conscious	?	Cold	Cyanosed	3	Raised	1

* W. H. died on the 9th day after admission. M. T. died on the 14th day after admission.

Four patients qualified for Group 3, two for Group 2, two for Group 1, and two for Group 0. The two patients who died were assessed as Group 3 (Case W. H.) and Group 4 (Case M. T.) risks respectively. Pain was present in all cases and its severity varied; it apparently depended to some extent on the level of consciousness of the individual. Only two patients were not sweating at the time of admission. Heart sounds were usually faint and a triple rhythm was heard in six. No pericardial rub was heard on admission, neither did it develop later in any of the patients. The jugular venous pressure was visible above the sternal angle in all patients except one (W. J.). On admission all the patients were able to lie recumbent without respiratory distress, and none complained of dyspnœa. There were isolated scattered crepitations at the lung bases in the Groups 2–4 patients.

Pulse Rate (Tables II and III, Fig. 1). On admission the pulse rate amongst the eleven patients ranged from 66 to 123 a minute (average 89 a minute). In seven of the nine who recovered, the pulse rate subsequently fell. The pulse rate varied inversely with the stroke volume in eight of the eleven patients studied, but as an isolated observation it gave little information of the clinical severity of the initial illness or of the stroke volume. Thus W. H. and M. T., who were clinically severely shocked on admission and who subsequently died, had pulse rates of 100 and 70 a minute respectively on admission, with stroke volumes of 57 and 71 ml. at that time. In contrast, L. N. and W. J., with no clinical signs of circulatory distress and pulse rates of 108 and 90 a minute on admission, had stroke volumes of 103 and 98 ml. respectively.

Blood Pressure (Tables II and III, Fig. 1). The mean blood pressure measured intra-arterially on admission ranged from 78 to 113 mm. Hg (average 98 mm. Hg). No obvious correlation existed between the mean blood pressure at the onset of the illness and the clinical severity of symptoms or the initial cardiac output. Amongst the nine patients who were studied again after recovery, four showed a rise in mean pressure associated with a rise in stroke volume. Three of these patients' pressures rose to hypertensive levels. The remaining five also showed a rise in stroke volume with recovery; this was associated with a fall in mean pressure. The initial clinical state of these patients was less shocked than was the state of the four patients whose mean pressure rose with recovery.

Pulse pressure on admission varied between 35 and 70 mm. Hg (average 50 mm. Hg). In six patients the pulse pressure increased following recovery and in three patients the pulse pressure decreased with recovery.

The initial mean pressures of the two patients who subsequently died (W. H. and M. T.) were 111 and 87 mm. respectively; the pulse pressures were 54 and 50 mm. Hg respectively.

TABLE II

ACUTE MYOCARDIAL INFARCTION

TABLE II

RESULTS IN ELEVEN PATIENTS STUDIED WITH ACUTE MYOCARDIAL INFARCTION

A: ON ADMISSION

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Patient	Time after first symptom	Sex	Age	Surface area sq. m.	Pulse per min.	S.V.C. pressure cm. H_2O	B.P. mm. Hg	Mean B.P. mm. Hg	Cardiac output l./min.	Cardiac index l./sq.m./min	Stroke vol. ml.	Mean circ. time sec.	I.T.B.V. litres	I.T.B.V. index l./sq. m./min.	Forearm blood flow ml./100 ml./min.	T.P.R. dyne.$^{-5}$ cm.	C/T ratio
L. N.	12 hours	F	47	1·75	108	+2·0	120/75	90	11·1	6·3	103	14·2	2·6	1·49	—	647	0·59
J. E.	16 hours	M	61	2·00	90	+2·0	140/90	107	8·8	4·4	98	22·8	3·3	1·67	1·5	970	0·56
W. J.	20 hours	M	48	2·20	90	−2·0	119/57	78	5·1	2·3	57	32·5	2·8	1·27	2·4	1212	0·57
G. C.	12 hours	M	45	1·80	123	+2·0	132/80	97	8·3	4·6	67	15·4	2·1	1·17	1·5	940	0·58
R. F.	19 hours	M	45	2·05	78	+3·0	132/80	98	7·1	3·5	92	26·7	3·2	1·55	1·7	1090	—
C. L.	20 hours	M	44	2·05	72	+0·5	120/90	100	6·0	2·9	83	22·3	2·2	1·07	1·4	1341	—
H. W.	4 hours	M	59	1·62	90	+4·0	150/90	110	7·1	4·4	79	14·1	1·7	1·03	2·3	1244	0·50
W. E.	6 hours	M	64	1·95	90	+2·0	160/90	113	4·8	2·5	53	29·0	2·3	1·19	—	1882	—
W. B.	4 hours	M	45	1·43	66	+5·0	105/70	82	4·2	2·9	63	31·0	2·4	1·50	2·0	1572	0·58
W. H.	16 hours	M	64	1·87	100	+1·0	150/96	111	5·7	3·0	57	18·2	1·7	0·92	2·6	1560	0·59
M. T.	10 hours	F	57	1·63	70	+4·0	120/70	87	5·0	3·0	71	38·7	3·2	1·96	—	1405	0·65
Average	12·6 hours		53	1·85	89	+2·1	132/81	98	6·7	3·7	75	24·8	2·5	1·34	1·9	1260	0·58

B: SUBSEQUENTLY

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Patient	Time after first symptom	Sex	Age	Surface area sq. m.	Pulse per min.	S.V.C. pressure cm. H_2O	B.P. mm. Hg	Mean B.P. mm. Hg	Cardiac output l./min.	Cardiac index l./sq. m./min.	Stroke vol. ml.	Mean circ. time sec.	I.T.B.V. litres	I.T.B.V. index l./sq. m./min.	Forearm blood flow ml./100 ml./min.	T.P.R. dyne^{-5} cm.	C/T ratio
G. C.	10 days				108	−3·0	140/70	93	10·1	5·7	93	11·5	1·9	1·08	3·6	738	
C. L.	9 days				76	−2·0	102/68	79	6·9	3·4	91	21·8	2·5	1·21	3·5	923	
H. W.	24 hours				96	+5·0	141/73	95	5·3	3·3	55	25·1	2·2	1·37	2·3	1444	
W. E.	5 days				90	+1·0	140/76	98	5·3	2·7	59	29·1	2·6	1·34	—	1470	
W. B.	13 days				64	−0·5	105/70	82	5·2	3·6	81	21·0	1·7	1·17	—	1267	
W. H.	6 days				90	+2·25	134/84	101	4·2	2·2	47	29·2	2·0	1·09	2·6	1925	0·54
,,	9 days				204*	+3·0	100/60	80		Not measured			1·6		Not measured		
M. T.	4 days				100	+6·5	149/89	109	4·9	3·0	49	23·1	1·9	1·17	2·2	1760	0·65

* The patient was studied during ventricular tachycardia. Venous pressure was assessed clinically. He died two hours later with ventricular fibrillation.

TABLE III

RESULTS IN NINE PATIENTS STUDIED FOLLOWING RECOVERY FROM ACUTE MYOCARDIAL INFARCTION

Patient	Time after first symptom	Sex	Age	Surface area sq. m.	Pulse per min.	S.V.C. pressure cm. H_2O	B.P. mm. Hg	Mean B.P. mm. Hg	Cardiac output l./min	Cardiac index l./sq. m. /min.	Stroke vol. ml.	Mean circ. time sec.	I.T.B.V. litres	I.T.B.V. index l./sq. m. /min.	Forearm blood flow ml./ 100 ml./ min.	T.P.R. $dyne^{-5}$ cm.	C/T ratio
L. N.	5 weeks	F	47	1·75	98	0·0	117/70	86	9·2	5·3	94	14·5	2·2	1·22	—	745	0·54
J. E.	8 weeks	M	61	2·00	87	0·0	200/70	153	8·1	4·1	102	22·5	3·0	1·53	3·8	1510	0·50
W. J.	5 weeks	M	48	2·20	80	−2·0	130/80	97	6·7	3·1	84	20·0	2·2	1·01	3·2	870	0·56
G. C.	5 weeks	M	45	1·80	105	−2·0	170/110	130	10·5	5·8	100	9·3	1·6	0·91	4·0	991	0·52
R. F.	4 weeks	M	45	2·05	90	0·0	150/90	110	8·8	4·3	98	14·1	2·1	1·01	3·8	817	—
C. L.	9 weeks	M	44	2·05	78	−5·0	130/82	98	9·2	4·5	118	13·5	2·1	1·01	2·2	852	—
H. W.	7 weeks	M	59	1·62	84	−3·5	136/82	100	7·0	4·3	83	17·0	2·0	1·22	4·0	1150	0·47
W. E.	4 weeks	M	64	1·95	70	−1·0	118/80	93	4·8	2·5	69	24·3	1·9	1·00	—	1544	—
W. B.	9 weeks	M	45	1·43	64	−4·0	100/60	73	4·8	3·4	75	21·0	1·7	1·17	5·7	1267	0·58
Mean					84	−1·9	139/80	93	7·7	4·1	88	17·4	2·1	1·11	3·8	1087	0·53
S. D.									2·00	1·04	13·4	2·4	0·20	0·11			
S. E.									0·67	0·35	4·5	0·8	0·07	0·04			

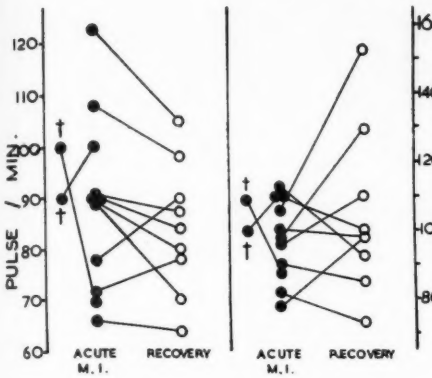

FIG. 1.—The pulse rate per minute, and mean blood pressure in mm. Hg following acute myocardial infarction, and after recovery. In this and subsequent figures, crosses indicate that the relevant patient died subsequently.

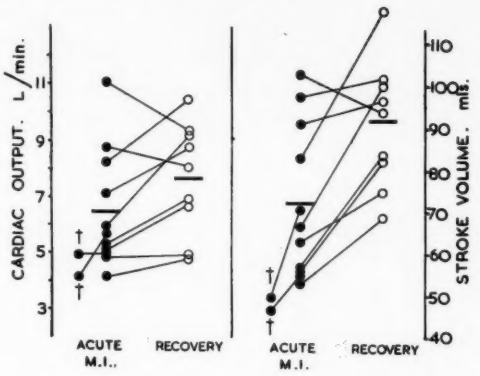

FIG. 2.—Cardiac output (l./min.) and stroke volume (ml.) following acute myocardial infarction and after recovery. In this and subsequent figures the thick horizontal lines, where present, indicate average figures for the appropriate group.

Cardiac Output (Tables II and III, Fig. 2). The initial minute cardiac output ranged between 4·2 and 11·1 l./min. (average 6·7 l./min.) and correlated with the clinical severity of the illness, being lower the severer the degree of circulatory collapse. Thus W. H. and M. T., who were admitted semi-conscious and collapsed, had a cardiac output of 5·7 l./min. and 5·0 l./min. respectively, while L. N. and J. E. who had few symptoms other than pain, had a cardiac output that was actually raised initially, being 11·1 l./min. and 8·8 l./min. respectively. In both the latter patients the cardiac output fell with recovery to 9·2 l./min. and 8·1 l./min. respectively.

The minute cardiac output rose following recovery in six of the remaining seven surviving patients, the seventh showing no change in cardiac output. (Average cardiac output on recovery was 7·7 l./min.) When expressed as stroke volume, all the patients except L. N. showed a rise in stroke output following recovery (average on admission 75 ml. per beat; average following recovery 88 ml. per beat). Case L. N. was a woman whose only symptom was pain and who was extremely alarmed by her symptoms. Her initial stroke output was raised (103 ml.); it fell towards normal after recovery (94 ml.). Cases W. H. and M. T., who were severely collapsed when initially studied and died nine and fourteen days later respectively, had initial stroke volumes of 57 ml. and 71 ml. respectively. W. H. when studied six days later showed a fall in cardiac output from 5·7 l./min. to 4·2 l./min., the stroke volume falling to 47 ml./beat. M. T., studied again three days after admission, showed a cardiac output of 4·9 l./min. at the expense of a fall in stroke volume from 71 to 49 ml./beat.

The reduction in cardiac output following acute myocardial infarction was compared with that occurring in a group of thirteen patients with left ventricular heart failure previously studied with Dr. H. Kopelman (Fig. 3). The two groups were not strictly comparable as the range of disability amongst the group with acute myocardial infarction was wide and the number studied too small to merit statistical analysis. However, in no instance was the reduction in cardiac output amongst the patients with acute myocardial infarction as great as that obtained in the group with left ventricular heart failure. The cardiac index ranged from 2·5 to 6·3 l./sq. m./min. (average 3·7 l./sq. m./min.) amongst the eleven patients studied with acute myocardial infarction: among the group with left ventricular heart failure the mean cardiac index was 1·95 l./sq. m./min.±0·12 l. The reduction in cardiac output still present in a second group of sixteen patients studied following recovery from left ventricular heart failure also tended to be greater than that obtained in the group studied following acute myocardial infarction, being 2·6 l./sq. m./min.±0·11 l. In the group of nine patients studied following recovery from acute myocardial infarction, cardiac output had risen to a range identical with that obtained from a group of ten normal subjects previously studied with Dr. Kopelman. (Following recovery from infarction: 4·1 l./sq. m./min.±0·91 l.; normal group: 4·1 l./sq. m./min.±0·35 l.)

Superior Vena Caval Pressure (Tables II and III, Fig. 4). In every case except one (W. J.) the jugular venous pressure was raised clinically on admission. All nine patients who recovered showed a fall in

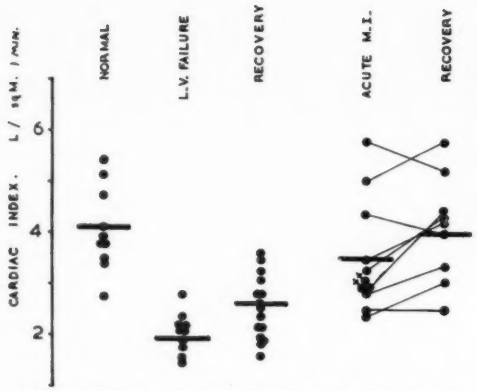

FIG. 3.—Comparison of cardiac indices (l./sq. metre/min.) between groups of (a) Controls, (b) left ventricular failure, (c) recovered from left ventricular failure, (d) acute myocardial infarction, (e) recovered from acute myocardial infarction.

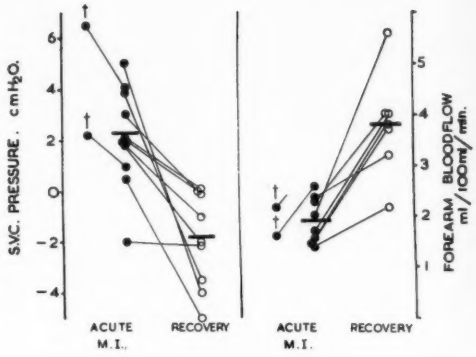

FIG. 4.—Superior vena caval pressure (cm. H_2O from sternal angle) and forearm blood flow (ml./100 ml. forearm/min.) in acute myocardial infarction and following recovery.

superior vena caval pressure ranging from 2 to 9 cm. H_2O (average 4·2 cm. H_2O). In the two patients who subsequently died (W. H. and M. T.) the superior vena caval pressure continued to rise after admission. Figure 5 shows the relationship between cardiac output, expressed as stroke volume, and central venous pressure measured from the superior vena cava. In some patients three separate estimations were made during the period in hospital. In all except one the stroke volume response to an increase in central venous pressure appeared to be decreased during the acute stage of the illness.

Forearm Blood Flow (Tables II and III, Fig. 4). Eight of the eleven patients admitted with acute myocardial infarction had forearm plethysmograph studies performed at the time of initial cardiac output estimation. Forearm blood flow ranged from 1·5 to 2·6 ml./100 ml. tissue/min. (average 1·9 ml./100 ml. tissue/min.). Seven patients were again studied following recovery; the forearm blood flow had risen in all cases and ranged from 2·2 to 5·7 ml./100 ml. tissue/min. (average 3·8 ml./100 ml. tissue/min.). Cases W. H. and M. T., who were studied at the time of admission but did not survive, showed low forearm blood flows (W. H. 1·6 ml./100 ml.; M. T. 2·2 ml./100 ml. tissue/min.).

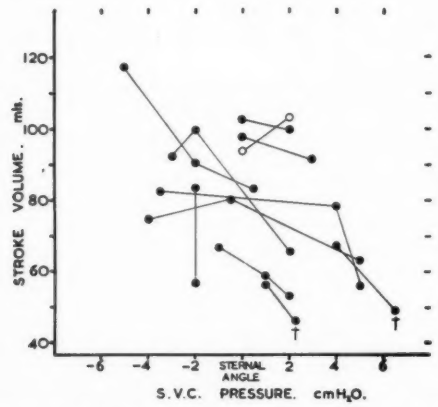

FIG. 5.—Relationship between stroke volume and superior vena caval pressure. Open circles represent Case L. N. (see Discussion).

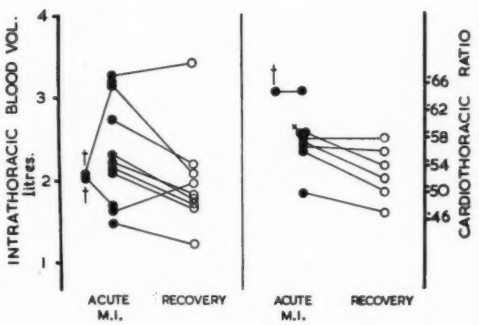

FIG. 6.—The intrathoracic blood volume (litres) and cardiothoracic ratio in acute myocardial infarction and following recovery.

Total Peripheral Resistance (Tables II and III).

$$\text{T.P.R.} \left[\frac{\text{Mean B.A. pressure} - \text{S.V.C. pressure (mm. Hg)}}{\text{Stroke volume (ml.)}}\right] \times 1332 \text{ dyne cm.}^{-5}$$

Calculated total peripheral resistance on admission varied between 647 and 1882 (average 1260) dyne cm.$^{-5}$. The peripheral resistance was highest in the most collapsed cases and continued to rise in the two patients who died. It fell in six of the nine patients who were studied again following recovery, being 745–1510 (average 1084) dyne cm.$^{-5}$ in this group. Two patients showed a rise in peripheral resistance following recovery (L. N. and J. E.); both these patients had a raised cardiac output on admission. One patient (G. C.) showed no significant change in peripheral resistance.

Intrathoracic Blood Volume (Tables II, III, Fig. 6 and 7). The circulating blood volume situated between the point of dye injection into the superior vena cava and the arterial sampling point was calculated

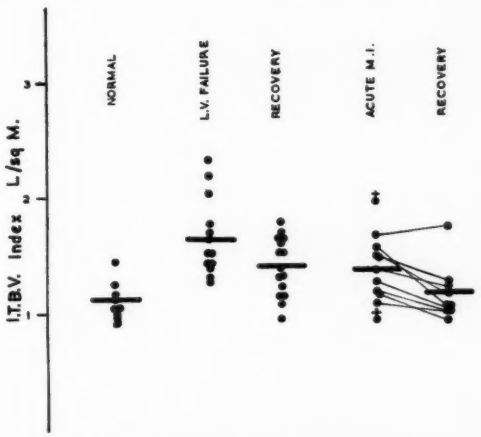

FIG. 7.—Comparison of intrathoracic blood volume indices (l./sq. m.) between groups of (a) Normals, (b) left ventricular heart failure, (c) recovered from left ventricular heart failure, (d) acute myocardial infarction, (e) recovered from acute myocardial infarction.

from the mean dye circulation time between the injection and sampling points, and the cardiac output. This volume was termed the " intrathoracic blood volume." The chief reservoirs composing this volume are the heart chambers and lung vessels. Changes greater than 200 ml. are probably significant by this method.

The intrathoracic blood volume index amongst the eleven patients studied with acute myocardial infarction ranged from 0·92 to 1·96 l./sq. m. (average 1·34 l./sq. m.). Though this group is not strictly comparable with a group of ten normal subjects previously studied (Kopelman and Lee, 1951) the intrathoracic blood volume was greater than in the normal group where the volume was 1·14 l./sq. m.±0·06 l. Following recovery, the intrathoracic blood volume fell towards normal values—ranging from 0·91 to 1·53 l./sq. m. (mean 1·11 l./sq. m.±0·04).

The intrathoracic blood volume during the acute phase of illness was smaller than either the group of patients studied with left ventricular heart failure (1·68 l./sq. m.±0·10 l.) or the group recovered from left ventricular heart failure (1·41 l./sq. m.±0·07 l.).

Heart Size (Tables II and III, Fig. 6). Accurate heart size measurement by simultaneous P.A. and lateral tele-radiograms were not undertaken, but the A.P. cardio-thoracic ratio was measured as a rough indication of heart size changes in eight patients. Meneely and Chesnut (1947) took a ratio of 0·54 as the upper limit of normal. In eight patients with acute myocardial infarction initial C.T. ratios ranged from 0·50 to 0·65. There was a slight fall in this ratio in six patients who were X-rayed again

following recovery (0·47–0·58). Patients W. H. and M. T., who subsequently died, had initial C.T. ratios of 0·59 and 0·65 respectively.

Discussion

The most consistent finding in the present study of acute myocardial infarction was an initially raised central venous pressure. This was clinically visible in the neck in all but one patient, and occurred whether or not there were clinical signs of shock. This clinical sign has been confirmed in a large number of similar patients examined since this study was completed. A typical history associated with a raised central venous pressure would appear to be as reliable for diagnosis as an abnormal cardiogram. This opinion differs from previous authors, who also reported a raised central venous pressure in acute myocardial infarction, but only when shock or cardiac failure was manifest (Fishberg *et al.*, 1934; Stead and Ebert, 1942; Freis *et al.*, 1952; Gilbert *et al.*, 1954; Smith *et al.*, 1954).

The present study only partly confirms previous workers' findings that the cardiac output is reduced in acute myocardial infarction, and that it is progressively lowered the severer the degree of shock (Grishman and Master, 1941; Hauss and Koppermann, 1950; Pritchard and Hellerstein, 1950; Freis *et al.*, 1952; Gilbert *et al.*, 1954; Smith *et al.*, 1954.) Amongst the eleven patients studied, two (L. H. and J. E.) with uncomplicated myocardial infarction, whose only apparent disability was pain, had initially raised cardiac outputs which fell following recovery: both had a raised central venous pressure. Calculated total peripheral resistance in both cases was low, initially suggesting vasodilatation, although forearm blood flow in J. E. was also reduced at that time. Both patients were extremely alarmed by their symptoms and possibly this type of cardiac response is explicable by a release of adrenalin acting upon a still responsive myocardium.

Among even the most severely collapsed patients cardiac output was surprisingly well maintained. The lowest cardiac output was 4·2 l./min. (2·2 l./sq. m./min.) from W. H. three days before his death from sudden ventricular fibrillation. Freis *et al.* (1952) and Smith *et al.* (1954) both report average cardiac indices from groups of patients with cardiogenic shock well below this figure; while the mean cardiac output in a group of patients studied with left ventricular failure, and quoted in the present report, was also slightly lower (1·95 l./sq. m./min.). However, it is possible that the present study was made on selected cases in that the most severely affected may have died before reaching hospital. But even M. T. and W. H., who were both admitted collapsed and who subsequently died, were able to maintain a reasonable cardiac output. Fig. 8 shows transverse sections of the ventricles of these two patients and reveals that in both cases half the circumference of the left ventricle contained recently infarcted tissue. In spite of this, W. H.'s cardiac output on admission was 5·7 l./min. (57 ml. per stroke), while M. T. had an initial cardiac output of 5·0 l./min. (71 ml. per stroke). However, Fig. 2 shows that the maintenance of minute cardiac output occurred at the expense of decreased stroke volume, which tended to be lowest in the most severely shocked patients and continued to fall as their condition deteriorated.

Evidence that the left ventricular response to changes in filling pressure had altered following acute myocardial infarction is only presumptive from the present data, because the assumption must be made that measured pressure changes in the superior vena cava reflect similar unmeasured changes in the left atrium. Such an assumption seems not unreasonable for Case *et al.* (1954) have shown in the dog that the left atrial pressure rises following myocardial ischæmia, produced by occlusion of the left main coronary artery. In the same experiments they showed that left ventricular stroke volume and stroke work progressively fell as the coronary flow was decreased, and under such circumstances they demonstrated a family of decreasing work response curves as left atrial pressure was increased. Fig. 5 shows that the stroke volume associated with the initial rise in central venous pressure was reduced at some early stage of the acute myocardial infarct in all cases except one, and rose subsequently in those who recovered. The lines connecting the closed circles in the figure serve only to link serial estimations of vena caval pressure and stroke volume during the course of each patient's hospital admission. They do *not* represent points on

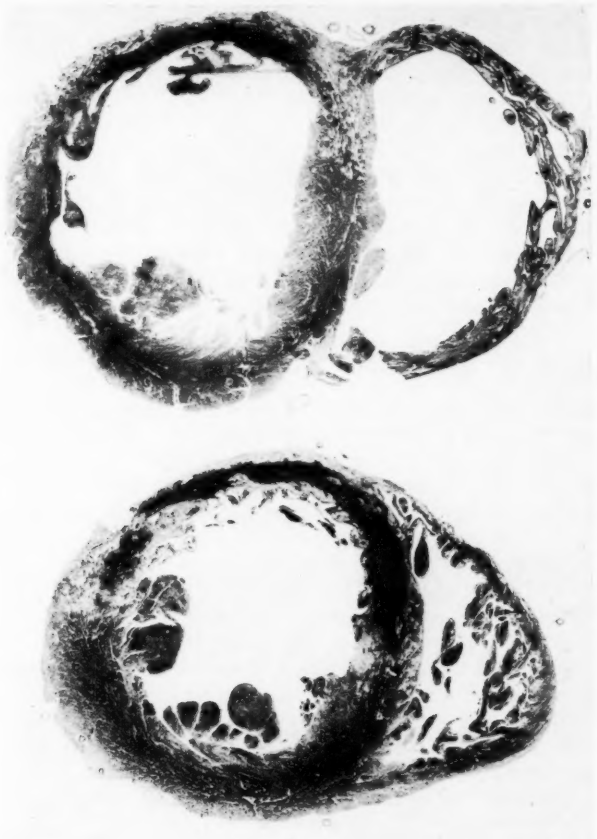

FIG. 8.—Transverse sections through the ventricles of Case W. H. above (cardiac output 5·7 litres/min.) and Case M. T. below (cardiac output 5·0 litres/min.). The sections show infarcted tissue, spreading through half the circumference of each left ventricle.

individual falling Starling curves as cursory examination of the figure might suggest, but on the contrary represent single points on a series of changing ventricular response curves (Case *et al.*, 1954) as the function of the myocardium altered during the course of the illness.

Further evidence that the myocardium did not respond normally to changes in venous filling pressure following acute infarction was obtained by use of the Valsalva manœuvre as a test. During the time that the patient's blood pressure was being recorded intra-arterially, he was asked to blow a mercury column to a height of 40 mm. Hg for ten seconds while the effect on the systemic blood pressure was recorded. During this period the raised intrathoracic pressure impairs systemic venous return to the heart and the central effective venous pressure falls (Lee *et al.*, 1954). In normal subjects this decreases stroke output and pulse pressure with consequent systemic reflex vaso-constriction and rise in diastolic pressure. Persistence of this vaso-constriction is largely responsible for the subsequent " overshoot " in blood pressure that follows the Valsalva manœuvre. However, in heart failure Sharpey-Schafer (1955) has shown that reduction in cardiac filling pressure

causes either no change or an increase in pulse pressure, and consequently the arterial pressure record has a square wave pattern with no " overshoot " following the Valsalva manœuvre, because no vaso-constriction has been initiated. Moreover, he has shown that similar changes to those found in heart failure occur initially in acute nephritis (Sharpey-Schafer, 1955), and that subsequent serial pressure records show a progressive return to the normal overshoot as the myocardium regains its normal response to changes in filling pressure.

Very similar changes were found in acute myocardial infarction. The most severely collapsed patient showed an initial heart failure blood pressure response to the Valsalva manœuvres (M. T., Fig. 9a). The response never became normal amongst those who recovered (H. W., Fig. 9b). Patients with intermittent grades of collapse (R. F. and G. C., Fig. 9c and 9d) gave either heart failure or impaired responses to the Valsalva manœuvre, and returned to normal following recovery. Only one patient gave a normal response initially to the Valsalva manœuvre; this was L. N., whose only symptom was severe pain and who also responded normally to a raised central venous pressure by a rise in stroke volume (Fig. 5—open circles).

Thus, in all but the mildest case there was functional evidence of myocardial failure, but in spite of a fall in cardiac output there was sufficient vaso-constriction, indicated by decreased forearm blood flow and increased peripheral resistance, to maintain the blood pressure in the recumbent position. The clinical signs of so-called " shock " therefore appeared to indicate homeostasis rather than circulatory failure. For these reasons it would seem that neither intravenous nor intra-arterial transfusion is advisable; and indeed study of previous experience of this form of treatment reveals a depressingly low survival rate and few objective measurements to support any impression of efficiency (Epstein and Relman, 1949; Silber *et al.*, 1951; Berman and Akman, 1952; Gootnick and Knox, 1953). However, suitable pressor amines given with the intent to raise blood pressure, increase coronary blood flow, and yet at the same time produce little change in cardiac output have greater theoretical and practical evidence of their merit (Kurland and Malach, 1952; Hellerstein *et al.*, 1952; Shirley Smith and Guz, 1953). Attempts to raise the oxygen tension in the border areas of infarcted myocardium by increased oxygen diffusion from normally perfused areas have been shown to be partly successful in limiting the size of the infarct. Sayen *et al.* (1951) accomplished this by raising the arterial oxygen tension in animals with experimentally produced myocardial infarcts by oxygen administration. This would seem useful therapy although Russek *et al.* (1950) could demonstrate no beneficial changes in the electrocardiogram nor any pain relief among patients with acute myocardial infarction treated with pure oxygen.

Two major paradoxes remain to be discussed. The first is that in spite of evidence of left ventricular failure, clinical signs of pulmonary œdema are absent in all but the most collapsed cases, and the small increase in intrathoracic blood volume that was found could well have been due to change in heart size alone (Fig. 6 and 7). This stimulates speculation regarding the mechanism preventing lung congestion and overt œdema in myocardial infarction. It is suggested that pulmonary capillary pressure probably rarely exceeds the critical level necessary to produce pulmonary œdema, and that this may be accomplished by a " Bernheim " effect resulting from sudden dilatation of the infarcted left ventricle. This would impair right ventricular function and result in some protection of the pulmonary system in spite of a failing left ventricle (Berglund *et al.*, 1955).

The second surprising finding was that neither the degree of systemic vaso-constriction, measured by decrease in forearm blood flow, nor the fall in cardiac output was as great as expected. Brigden and Sharpey-Schafer (1950) have shown that intense systemic vaso-constriction is the rule in left ventricular heart failure and that the forearm blood flow rarely rises above 1·0 ml./100 ml./min. Acute coronary occlusion differs from other causes of heart failure in producing sudden injury and death of myocardium. This may well be accompanied by release of vasodilator substance from the infarcted area, or by reflex vasodilatation. For instance, the Bezold reflex initiates bradycardia and systemic vasodilatation when afferent fibres from the ventricles are stimulated by chemical injury or pressure increase (Dawes, 1947; Jarisch and Zotterman, 1949; Dawes *et al.*,

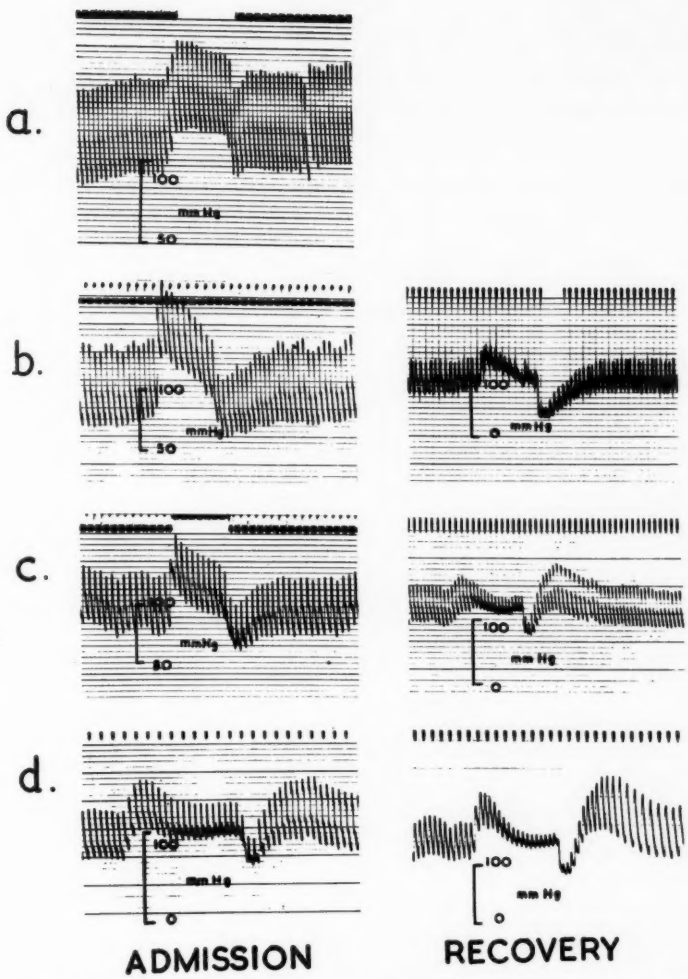

FIG. 9.—The blood pressure responses to Valsalva's manœuvre in patients with acute myocardial infarction and following recovery. Time marker shown recording seconds.

(a) Case M. T.: initial heart failure response; subsequently died.
(b) Case H. W.: modified heart failure response which did not become normal following recovery.
(c) Case R. F.: modified heart failure response; normal response following recovery.
(d) Case G. C.: Almost normal initial response, becoming completely normal following recovery.

1951). Afferent stimulation from the infarcted or neighbouring ischæmic areas might similarly cause vasodilatation and tend to counteract vasoconstriction initiated by the decrease in stroke volume that follows myocardial infarction.

Summary

Eleven patients admitted to hospital following acute myocardial infarction have been studied. In nine, further studies were performed following recovery. Two patients died.

Pulse and blood pressure measurements alone were unhelpful in assessing clinical severity, and signs of pulmonary congestion were minimal.

The central venous pressure was raised in all but one patient. Cardiac output was reduced in all but two patients, and was lowest in those clinically most collapsed. It returned to normal following recovery. It was not as greatly reduced in myocardial infarction as in a group of patients with left ventricular heart failure. Forearm blood flow was reduced to approximately half normal, and rose following recovery. Intrathoracic blood volume was slightly increased and returned to normal limits following recovery. There was also a slight increase in heart size.

I am most grateful to Dr. R. Hilton, Dr. H. K. Goadby, Dr. J. B. Harman, and Dr. J. S. Richardson for permission to study the patients under their care. I wish to thank Dr. B. E. Miles, Dr. H. B. Kelly, and Dr. P. Handforth for assistance at the bedside, and am grateful to Mr. M. E. Dunn for his technical help.

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THE GRAPHIC CONFIGURATION OF INNOCENT SYSTOLIC MURMURS

BY

BERTRAND WELLS

From St. Bartholomew's Hospital and the National Heart Hospital

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The systolic murmurs heard in healthy subjects used to be called "functional" murmurs. White *et al.* (1942) recommended the term "physiologic." Evans (1947) called these murmurs "innocent." Others have called them "incidental," "accidental," or "murmurs of unknown origin."

The decision that a systolic murmur is innocent usually depends not only on the character of the murmur itself, but also on the absence of any evidence of organic heart disease. The improvement in the technique of phonocardiography during the last decade provides a means whereby the innocent systolic murmurs can be studied more objectively. Such a study should lead to more accurate diagnosis, to a more useful classification, and perhaps to an explanation of the production of these murmurs. Bass *et al.* (1933) found that innocent systolic murmurs were composed only of high-frequency vibrations and this differentiated them from organic murmurs which were composed of both low- and high-frequency vibrations. Evans (1948) clearly demonstrated the brief duration of innocent systolic murmurs by phonocardiography, and later (1951) he stated that "A detection of the frequency of the separate murmurs may also contribute to a readier recognition of the innocent ones from amongst the others." Evans (1948) also described the phonocardiogram of the late systolic murmur. Harris *et al.* (1949) studied the phonocardiogram of children with mitral regurgitation and children with innocent systolic murmurs; they described the short duration and "vibratory" nature of the innocent murmur, and noted the similarity of pattern to that produced by a tuning fork. Harris and Friedman (1952) collected 28 tracings of "vibratory" systolic murmurs in children, and Boldrini *et al.* (1954) added a further 20 tracings. The latter workers found the duration of the murmur was between 0·07 and 0·12 seconds. Other workers (Wood, 1950; Gmachl, 1953; and Wells, 1954) have published tracings of innocent systolic murmurs.

The object of the present study is to describe the appearance on the phonocardiogram of innocent systolic murmurs. The appearance should be of value in the diagnosis and explanation of innocent systolic murmurs, and should help in the differentiation of such murmurs from the murmurs of organic heart disease.

MATERIAL

The study consists of the clinical and phonocardiographic findings in 70 healthy subjects. Their ages varied between 5 and 56 years, and 36 were males and 34 females. They are consecutive cases on whom phonocardiograms were taken when there was a clinical diagnosis, supported by X-ray screening and electrocardiography, of innocent systolic murmur. Ten of the subjects had a murmur in late systole in the mitral area. There is some evidence that subjects with this murmur may later develop subacute bacterial endocarditis or mitral incompetence (Brigden and Leatham, 1953). Their innocent nature has been assumed by Evans (1948), and has been assumed in this study because such a murmur has never been found in 1000 phonocardiograms on patients with heart disease.

The material is not unselected because phonocardiograms were not taken on every subject with an innocent systolic murmur. It is therefore possible that the preponderance of innocent systolic murmurs in the mitral and præcordial areas is partly due to the fact that the innocent murmurs in the pulmonary area are more easily dismissed as of no importance. It is also possible that the cases chosen include an undue proportion of murmurs of moderate intensity rather than those of slight intensity. In no case was the murmur clinically louder than Grade 3 (grading of Levine, 1933).

In order to contrast innocent murmurs with the murmurs of organic heart disease 18 cases of aortic stenosis have been analysed in a similar way. The patients were between 6 and 77 years of age, and 11 were males and 7 females.

Method

The tracings were taken on a Sanborn phonocardiograph using a logarithmic frequency response and a paper speed of 75 mm. a second. The routine locations for the microphone were the mitral and pulmonary areas and the fourth left interspace at the left sternal border, and also the area of maximal intensity of the murmur. The gain of the amplifier was not altered when the microphone was moved from one location to the next so that the relative intensity of the murmur might be estimated from the tracings. At least eight heart beats were recorded at each location so that the non-cardiac vibrations could be identified. The precautions necessary to obtain satisfactory tracings have been described earlier (Wells *et al.*, 1949).

The timing of the murmur in systole was measured from the onset of the maximal vibrations of the first heart sound. This is the beginning of the second component of the first heart sound and represents the time of closure of the mitral valve. The intervals measured were from this point to the beginning and end of the murmur, to its point of maximal intensity, and to the beginning of the second heart sound. The last figure was taken as the duration of systole, and was recorded together with the cycle length taken from the synchronous electrocardiogram.

The frequency of the vibrations constituting the murmur was measured by counting with the help of a hand lens the number of waves in one-tenth of a second. Vibrations that were slurred were counted as single, and vibrations that were distinctly notched were counted as two.

No measurement has been made of the absolute intensity of the vibration, or of their intensity relative to the heart sounds.

Results

The seventy cases fall into three main groups. They are distinguished by the location of the maximal intensity and by the graphic configuration of the murmur.

(1) *Innocent præcordial murmurs*, occurring in an area from just within the apex beat to the left sternal border between the third and fifth intercostal spaces. They are divided on phonocardiographic appearances into two groups.

Coarse variety, composed of uniform vibration of low frequency. The vibrations start early in systole and usually rise smoothly and rapidly to a maximal intensity which is slightly earlier in systole than is the case in aortic stenosis. The intensity usually falls off as smoothly though less rapidly, and the murmur ends before or just after mid-systole. This coarse variety of innocent præcordial murmur is that described by Harris as "vibratory." Examples of the murmur are shown in Fig. 1.

Fine variety, composed of irregular vibrations of intermediate frequency. These murmurs resemble the ejection murmurs of aortic or pulmonary stenosis except for the fact that they are of shorter duration and are slightly earlier in systole. Examples are shown in Fig. 2.

(2) *Late systolic murmurs*, all of which are maximal in the mitral area. They are composed of high-frequency vibrations starting after mid-systole and increasing in intensity in a crescendic manner. The reasons for considering these murmurs innocent have already been stated. Examples of these murmurs are shown in Fig. 3.

(3) *Innocent murmurs in the pulmonary area*, having their maximal intensity in the second left interspace, and being composed of vibrations of intermediate frequency. These murmurs resemble the fine variety of innocent præcordial murmur except that they are of longer duration. The duration is, however, shorter than that of the murmur of aortic stenosis. Examples of innocent murmurs in the pulmonary area are shown in Fig. 4.

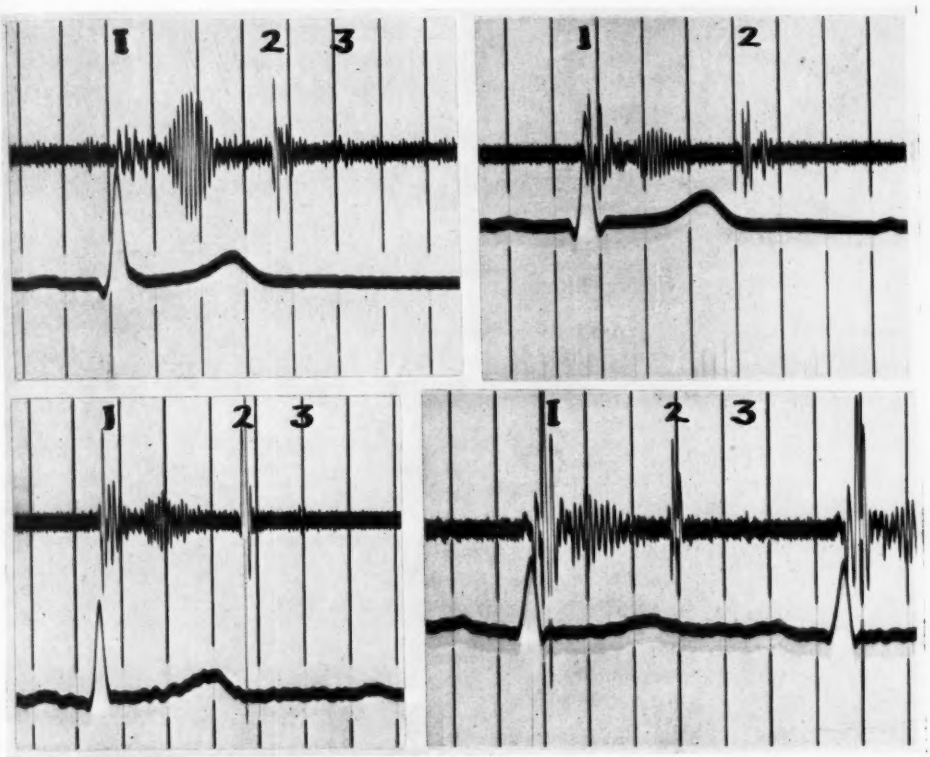

FIG. 1.—*Coarse Variety of Innocent Præcordial Murmur.* Logarithmic phonocardiograms of four subjects with innocent præcordial murmurs of the coarse variety, showing regular vibrations of low frequency. Reference tracings electrocardiogram, lead II. Time lines 0·1 sec.

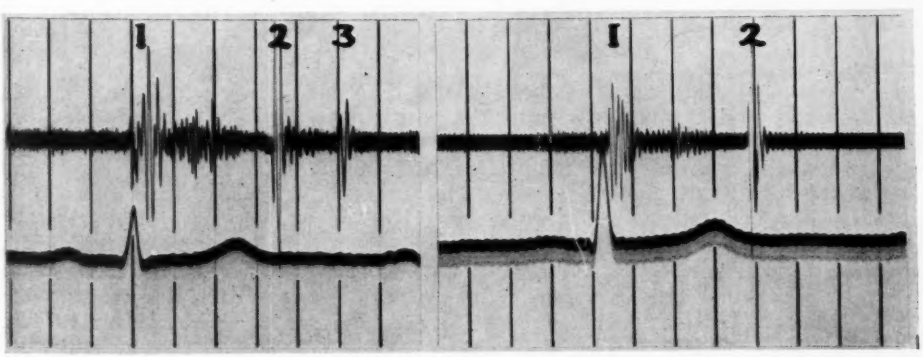

FIG. 2.—*Fine Variety of Innocent Præcordial Murmur.* Logarithmic phonocardiograms of two subjects with innocent præcordial murmurs of the fine variety, showing irregular vibrations of intermediate frequency. Reference tracings as for Fig. 1.

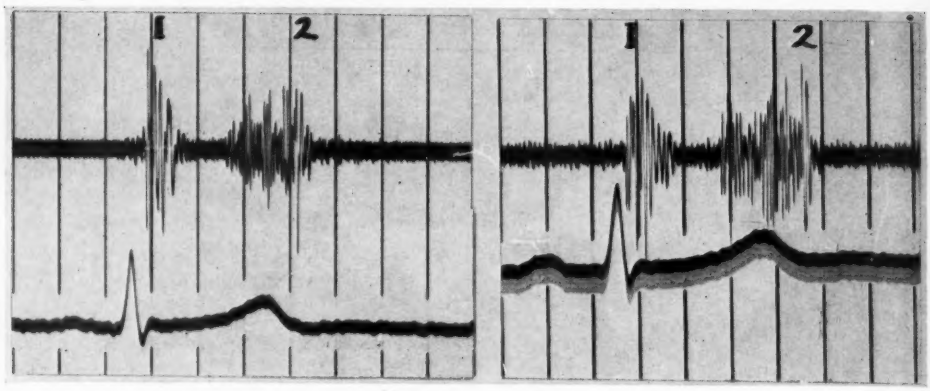

FIG. 3.—*Late Systolic Murmurs.* Logarithmic phonocardiograms of two subjects with late systolic murmurs. The vibrations are of high frequency and do not start until the second half of systole. Reference tracings as for Fig. 1.

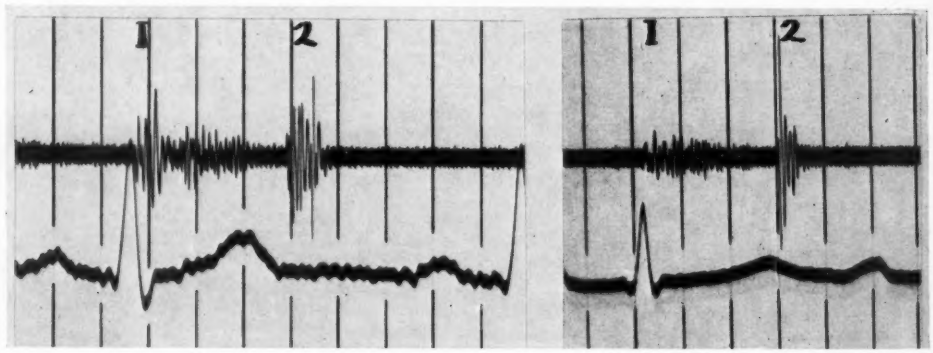

FIG. 4.—*Innocent Systolic Murmurs in the Pulmonary Area.* Logarithmic phonocardiograms of two subjects with innocent systolic murmurs in the pulmonary area. The vibrations are irregular and of intermediate frequency and of slightly longer duration than in the other innocent systolic murmurs. Reference tracings as for Fig. 1.

The *age* of the patients in each group is shown in the Table. The only inference that may be drawn from such a series is that each murmur may be found at any time from childhood to adult life. Evans (1955) believes that the only innocent systolic murmurs heard after the age of 40 are the murmurs in late systole. There are two exceptions to this in the present series. The first is a man of 48 with a coarse præcordial systolic murmur and no evidence of heart disease: such a murmur might readily be attributed to aortic sclerosis (deformity of the aortic valve cusps without narrowing), but in this case it was considered innocent because it was coarse and brief, and showed on the phonocardiogram as regular vibrations of low frequency. The second exception is a woman of 56 with a brief præcordial murmur in early systole; in this case the murmur was considered innocent because it had been present for twenty years without evidence of heart disease.

The *duration* of all innocent systolic murmurs is brief. The longest murmur is that in the pulmonary area and this murmur is of shorter duration than the murmur of aortic stenosis. The murmur of aortic stenosis has a duration of between 0·18 and 0·25 sec., while that of the innocent murmur in the pulmonary area is between 0·15 and 0·20 sec. The innocent præcordial murmur

TABLE

Table showing the age of the subjects, the time relationships of the murmurs, and the frequency of the vibrations in cycles a second. The upper figures are mean values and the lower figures in brackets are the maximum and minimum values

Type of murmur	No. of cases	Age of patients	Length of murmur	Length of systole	Length of cycle	Onset of murmur	End of murmur	Peak of intensity	Frequency of murmur
			(In hundredths of a second)						
Præcordial: Coarse variety	40	14 (3–48)	10 (8–13)	32 (25–38)	84 (59–135)	10 (5–12)	20 (14–25)	15 (9–18)	110 (75–160)
Fine variety	10	29 (2–56)	11 (9–12)	32 (23–38)	81 (47–105)	9 (5–13)	20 (15–22)	14 (10–16)	170 (120–240)
Late systolic	10	32 (11–51)	14 (12–17)	35 (30–39)	97 (70–115)	21 (20–22)	35 (30–49)	29 (25–35)	220 (200–260)
Pulmonary	10	16 (5–30)	16 (15–20)	31 (26–35)	80 (65–96)	8 (5–10)	24 (23–25)	15 (8–18)	170 (130–230)
Aortic stenosis	18	36 (6–77)	21 (18–25)	33 (30–36)	87 (64–120)	6 (4–11)	27 (25–30)	17 (12–20)	210 (180–300)

and the late systolic murmur are so brief that this is one of their most characteristic features. The longest of these murmurs is 0·17 sec. which is shorter than the shortest murmur of aortic stenosis (0·18 sec.).

The *timing* in the cardiac cycle is an important feature of innocent systolic murmurs. The late systolic murmur can be immediately identified because it does not start until the second half of systole. The other innocent murmurs begin early in systole and occupy more of the first half of systole than the second half. This usually enables these murmurs to be differentiated from murmurs of organic heart disease. In every case in this series the murmur ends within 0·25 sec. after the beginning of the major vibrations of the first heart sound, and in none of the cases of aortic stenosis did the murmur end before this time.

The *maximal intensity* of the late systolic murmur is near the second sound. In the other innocent systolic murmurs the maximal intensity is usually before mid-systole. Although this feature does not help much in differentiating an innocent murmur from a murmur of organic heart disease it may throw light on the mode of production of the murmur.

The *frequency of the vibrations* constituting the innocent systolic murmur is interesting. The late systolic murmur has a high frequency of between 200 and 260 cycles a second. This is the same frequency as is found in the murmur of mitral regurgitation. It would be tempting to attribute the late systolic murmur to a fine regurgitant stream through the mitral valve. In further support is the fact that the murmur of mitral regurgitation is sometimes louder in the second half of systole than the first. Despite these findings a genuine late systolic murmur (that is one in which the phonocardiogram shows no murmur in early systole) has been considered innocent. This is because it was never found in conjunction with evidence of mitral valve disease or of cardiac enlargement.

The coarse variety of innocent præcordial murmur is composed of low-frequency vibrations between 75 and 160 cycles a second. Moreover, the vibrations are quite regular and contain no high-frequency components at all. This pattern is pathognomonic of an innocent murmur. It suggests that the murmur is not due to turbulence of the blood, but that it comes from a vibration of the heart muscle itself. Regular vibrations of low frequency are never found in organic heart disease, although regular vibrations of high frequency occur in cases of rupture of an aortic or mitral valve cusp.

The fine variety of innocent præcordial murmur is composed of irregular vibrations of intermediate frequency (120 to 240 cycles/sec.). It is maximal below the pulmonary area and of shorter duration than the murmur in the pulmonary area, but not distinguishable in any other way. The close resemblance of these murmurs suggests that they are produced in a similar way. This is probably a turbulence in the blood stream at the time of rapid increase in the rate of blood flow.

Discussion

The three types of innocent systolic murmur that are described in this study constitute the simplest classification possible from the point of view of phonocardiography. The change in these murmurs with posture and respiration is an important feature in auscultation, but it is possible to establish the innocent nature of the murmurs by phonocardiography without such manœuvres. The frequent occurrence of the coarse variety of præcordial murmur explains the buzzing or twanging character so often heard on auscultation. The uniform and low frequency of the vibrations explains the changes often noted when the pressure of the chestpiece of the stethoscope on the skin is varied. It is for this reason that the murmur is sometimes considered to be exocardial. The nature of the vibrations suggests, however, that they come from the heart wall during ventricular contraction. When the murmur is loud it may often be mistaken for the murmur of ventricular septal defect.

Summary

Seventy healthy subjects with innocent systolic murmurs have been studied by phonocardiography in order to establish the value of this investigation in the diagnosis, classification, and explanation of these murmurs. Eighteen patients with aortic stenosis have been studied in the same way in order to contrast the innocent murmurs with those of organic heart disease.

The inocent murmurs fell into three groups.

(1) *Innocent præcordial murmurs* of brief duration ending soon after mid-systole. These were divided on phonocardiographic appearances into coarse and fine varieties depending on the frequency of vibration.

(2) *Late systolic murmurs*, confined to the mitral area, not beginning until mid-systole, and composed of high-frequency vibrations.

(3) *Innocent murmurs in the pulmonary area*, often with some accentuation and delay of the pulmonary component of the second heart sound. The vibrations do not differ from those of the fine variety of præcordial murmur, but the duration of the murmur is slightly longer.

The phonocardiogram is of value in the diagnosis of innocent systolic murmurs. The pattern of the coarse variety of præcordial murmur is characteristic and prevents the erroneous diagnosis of pulmonary or aortic valve disease, or even of ventricular septal defect. The late systolic murmur can only be accepted as innocent when in the tracing the first half of systole is quite free from any murmur.

I am very grateful to Dr. Geoffrey Bourne and Dr. William Evans for their help and advice, and for their permission to describe the patients who were under their care.

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CASE REPORTS

CONGENITAL ARTERIOVENOUS FISTULA OF THE INTERNAL MAMMARY VESSELS

BY

B. G. WELLS AND R. L. HURT

From St. Bartholomew's Hospital

Elkin and Warren (1947) have described traumatic arteriovenous fistulæ in practically every named blood vessel of the body with the exception of the aorta. Congenital arteriovenous fistulæ are much less common. Thus Callander (1920) found only three congenital cases in a series of 447 arteriovenous fistulæ. The usual location of congenital arteriovenous fistulæ in the systemic circulation is in the extremities, or head and neck. Pemberton and Saint (1928) believed that the trunk was rarely if ever affected. Adams (1951) described congenital arteriovenous fistulæ of the pancreas, spleen, and kidney, but none in the thorax. Johnson (1954), and Peräsalo and Kyllönen (1954), have described congenital arteriovenous fistulæ of the subclavian vessels simulating patent ductus arteriosus. Maier and Stout (1950) report a case of congenital arteriovenous fistula of the internal mammary vessels with a hæmangioma of the pectoralis major muscle. Other cases of hæmangioma and arteriovenous fistula of the chest wall have been reported by Takaro and Claggett (1951).

Case History

The patient, a woman aged 34, had suffered from asthma for many years and in 1942 had been admitted to St. Bartholomew's Hospital under the care of the late Dr. A. E. Gow for investigation of this. No cardiac abnormality was noted at this time. In 1948 she was again admitted to hospital, and for the first time a præcordial murmur resembling that of patent ductus arteriosus was heard: surgical treatment was not advised. In 1954 she began to complain increasingly of dyspnœa on exertion, and because of this an operation to close the presumed ductus was thought advisable. In retrospect, however, it would seem that her dyspnœa was due to her asthma rather than her cardiovascular lesion.

Clinical examination showed there to be a thrill palpable over the second left interspace, and a continuous high-pitched murmur was audible over the same area. The phonocardiogram showed that the vibrations were higher in frequency and more constant in intensity than is usual in patent ductus (Fig. 1). There was no cyanosis or clubbing of the fingers. There was no enlargement of the subcutaneous veins on the front of her chest. The blood pressure was 130/70. The blood count was normal. The chest radiograph showed a heart of normal size and shape, and the lung fields appeared normal. The electrocardiogram was normal.

Because no abnormality had been noted in 1942 it was thought that the diagnosis of patent ductus arteriosus should be confirmed by cardiac catheterization. Although the catheter could not be passed through a patent ductus the oxygen content of the blood in the left pulmonary artery exceeded by 1·88 vols. per 100 ml. that of the right ventricle, and by 1·67 vols. that of three samples from the main pulmonary artery. This was considered sufficient confirmation of the clinical diagnosis.

At operation on 10/3/55 (R.L.H.) the expected thrill over the pulmonary artery could not be felt, and a dissection of the interval between the pulmonary artery and the aorta showed a normally obliterated ductus arteriosus. It was then noticed that the internal mammary vessels were enlarged and tortuous in their course from the superior mediastinum to the second intercostal space, at which point there was an arterio-venous fistula. A thrill could be palpated over this fistula, and it was abolished by compression of the internal mammary artery proximally. A phonocardiogram and electrocardiogram were taken at the time of operation whilst the internal mammary artery was compressed proximal to the fistula. The vibrations on the phonocardiogram were similar to those previously recorded from the chest wall, showing a frequency of 270 cycles per second. They were completely stopped by compression of the internal

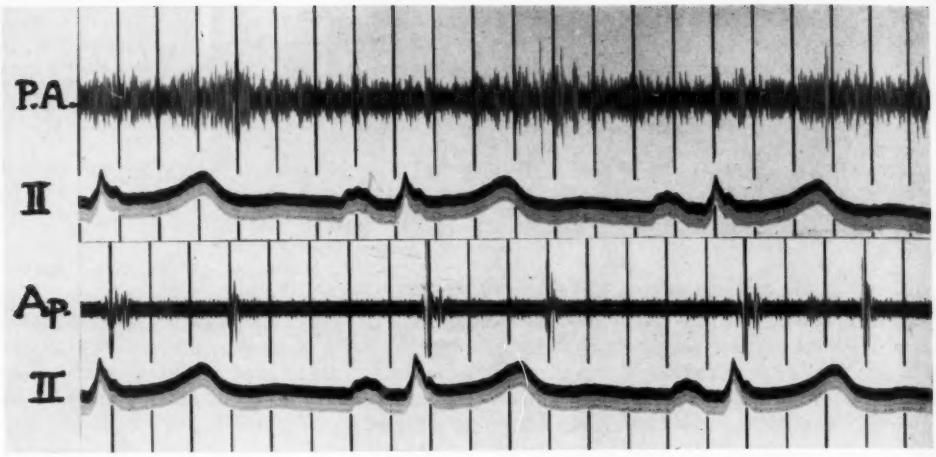

FIG. 1.—Logarithmic (high frequency) phonocardiograms of the continuous murmur in the pulmonary area (P.A.), and of the heart sounds at the apex (Ap.). The reference tracing (II) is Lead II of the cardiogram, and the time lines 0·1 sec. The frequency of the vibrations (270 cycles/sec) is higher, and their intensity is more uniform, than is usual is patent ductus arteriosus.

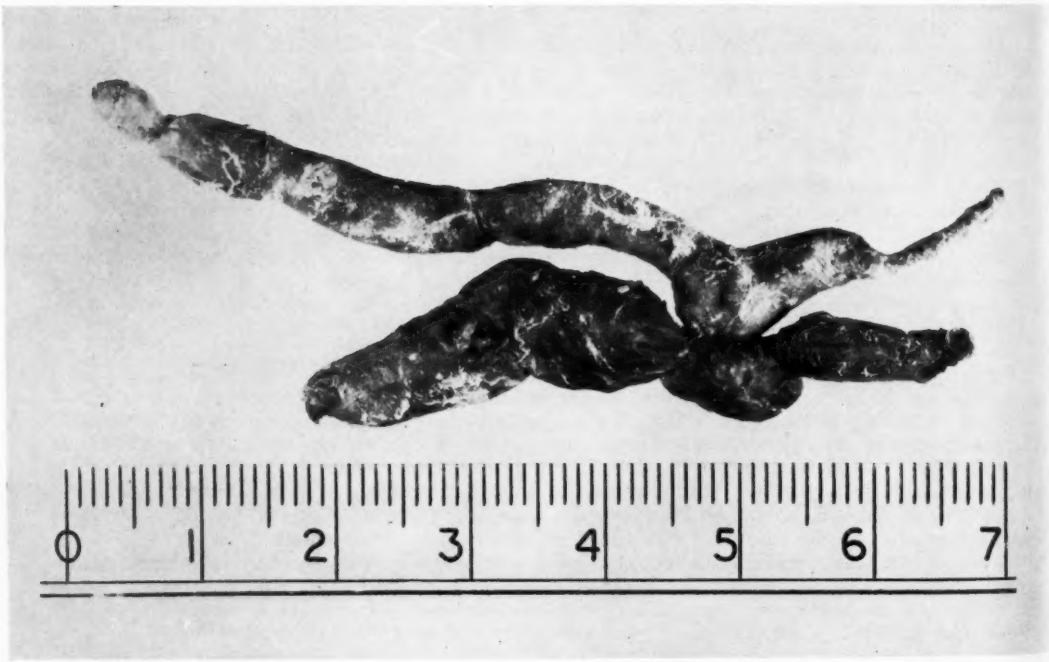

FIG. 2.—The internal mammary vessels with the arteriovenous fistula after excision.

mammary artery proximal to the fistula, while the electrocardiogram showed some slowing of the heart rate each time this manœuvre was performed.

The internal mammary vessels entering and leaving the fistula were ligated, and the aneurysm was excised. The appearance of the specimen is shown in Fig. 2. The patient's convalescence was uneventful.

Discussion

The character of the murmur was not typical of patent ductus arteriosus. The murmur had the characters of the murmur of systemic arteriovenous fistula described by Edwards and Levine (1952). However, there was no history of trauma, and no pulsation was palpable as in the case of Maier and Stout (1950).

The absence of cyanosis and clubbing, and the normal lung shadows on the X-ray film suggested that the case was not one of pulmonary arteriovenous fistula. Moreover, the acyanotic case of pulmonary arteriovenous fistula described by Salvesen and Marstander (1951) had no murmur.

The possibility of a coronary arteriovenous fistula was considered, but the cases described by Halpert (1929), Biorck and Crafoord (1947) and Paul *et al.* (1949) indicate that the diagnosis is difficult without thoracotomy. Wood (1950) states that the oxygen content in samples from the coronary sinus should be unusually high.

The murmur of rupture of a sinus of Valsalva into one of the cavities of the heart was also considered. This usually results in a communication between the right coronary sinus and the right ventricle. The murmur is usually lower than that of patent ductus arteriosus, and ceases to be continuous when the right ventricular pressure rises. There is usually progressive enlargement of the heart, and the prognosis is bad. The longest reported survival is that of a woman who lived 17 years after the rupture occurred (Morgan Jones and Langley, 1949).

The cardiac catheterization gave a false confirmation of the clinical diagnosis of patent ductus arteriosus.

When the history of the case is examined in conjunction with the operative findings it is reasonable to assume that the continuous murmur was not present when the patient was 21 years of age. This supports the postulate of Lewis (1930) that the presence of a congenital arteriovenous fistula may not become manifest until late in life.

Summary

A case of congenital arteriovenous fistula of the internal mammary vessels is described.

A diagnosis of patent ductus arteriosus was made despite several unusual features, and was later proved to be incorrect. Thoracotomy was performed at the age of 34 owing to increasing dyspnœa on exertion, although this was possibly due to asthma.

The arteriovenous fistula was removed by quadruple ligation and excision.

We are most grateful to Mr. O. S. Tubbs and to Dr. G. W. Hayward for their permission to publish this case.

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RUPTURE OF AN ANEURYSM OF THE RIGHT AORTIC SINUS (OF VALSALVA)

BY

LEONARD WEISS

Formerly of the Department of Pathology, Chase Farm Hospital, Enfield

Direct intrapericardial rupture of a congenital aneurysm of the sinus of Valsalva is a rare event. Rupture is said to occur most commonly between the ages of 14 and 30 years (Abbott, 1919). The following case is considered worthy of note, partly on account of the advanced age of the patient.

Case Report

The patient was a woman aged 72 years. She was said to have been in good health. While having breakfast she suddenly " collapsed ". She remained comatose until she died, some 48 hours after the onset of symptoms. The patient came from an Old People's Home, and it was not possible to obtain a more detailed clinical history.

Necropsy Findings. The pericardium was distended with about 200 ml. of blood. Within the pericardial sac was a saccular aneurysm of about 8 cm. diameter, which arose from the ascending aorta in the region of the right aortic sinus of Valsalva. The sac competely covered the anterior surface of the right atrium, and was firmly adherent to it. The superior aspect of the sac was adherent to the pericardium. In the ascending aorta were two foramina communicating with the sac; these had smooth rounded edges (Fig. 1) and the superior and inferior foramina were 1 cm. and 2 cm. in diameter, respectively. (The black marker in the photograph goes through the superior foramen, into the aorta.) The sac was 2 mm. thick, and was lined by organizing thrombus, 1 to 2 mm. deep. In the right inferior wall of the sac was a linear tear, 1 cm. long; this was the site of the rupture. The muscle of the right atrium and left ventricle was hypertrophied. The valves, septa, and great vessels were normal. There was *no* direct channel of communication between the sac and any of the chambers of the heart. There was a moderate degree of pulmonary œdema. The liver and spleen were congested. The kidneys showed minimal atheromatous change.

Histological sections of the sac show it to be composed mainly of fibrous tissue, with scant amounts of elastic and muscular tissues. Sections of the thoracic and abdominal aortæ show minimal atheromatous change. There was no evidence of syphilitic aortitis or medio-necrosis.

Discussion

The points of special interest in the case described, are as follows.

First, the advanced age of the patient (72 years). Abbott (1919) gives the average upper age limit as 30 years. The oldest case in Goehring's (1920) series was aged 41 years, and Ostrum *et al.* (1938) describes one aged 49 years. It would appear that the upper age limit given by Abbott is extremely flexible. Realization of this may help in the diagnosis of the condition during life. This is of increasing importance, as advances in cardiac surgery may soon permit the repair of such aneurysms.

Secondly, the presence of two foramina in the aorta, each communicating with the sac. This suggested that the sac was possibly the end result of a recanalized dissecting aneurysm. Against this, however, is the fact that the rest of the aorta was normal on naked-eye and microscopical examination. Had a dissecting aneurysm occurred, then patches of medio-necrosis or atheromatous plaques would be expected elsewhere in the aorta. A patch or plaque occurring at the site of the aortic sinus, and nowhere else, is extremely unlikely. In the absence of positive pathological findings, the foramina must both be regarded as congenital anomalies.

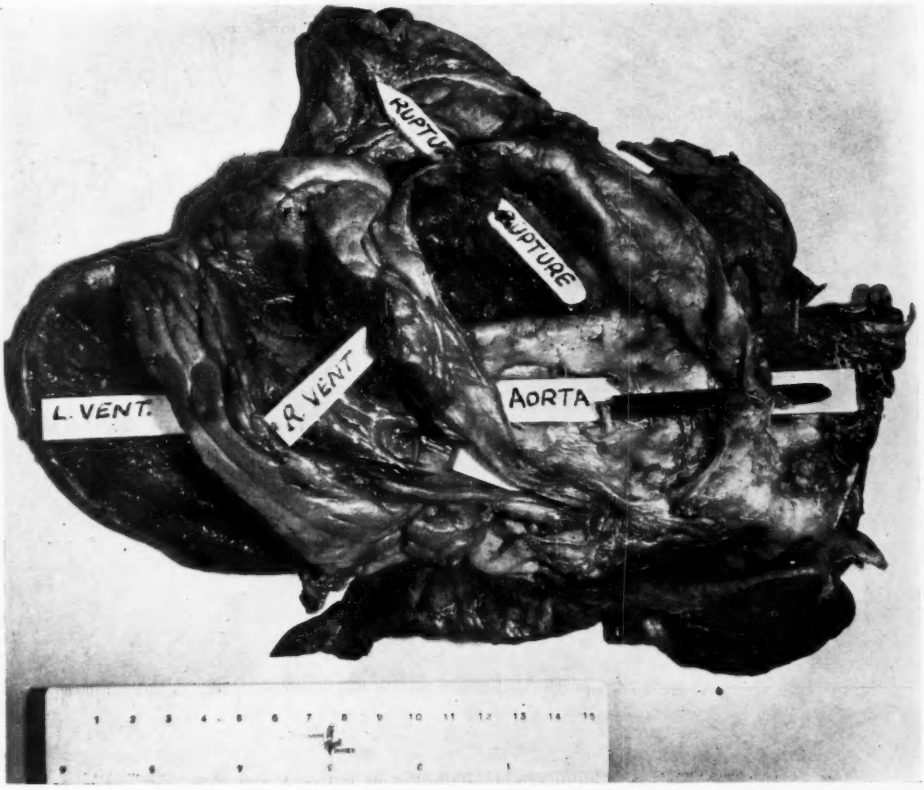

FIG. 1.—Anterior surface of dissected specimen, showing markers going through the site of rupture, and in the aortic foramina.

Thirdly, the long (48 hours) interval between rupture of the sac and death, assuming the rupture was heralded by the onset of unconsciousness. Of two cases reported of the rupture of mycotic aneurysms in this region (Ostrum *et al.*, 1938), death was sudden in the first case and due to hæmopericardium. In the second case, the rupture orifice was small, and leakage into the pericardium was slow, with a resulting plastic pericarditis. In the present case, perhaps a factor in retarding the flow of blood into the pericardium was the presence of two aortic orifices. The superior orifice may have acted as a safety valve for the release of pressure within the sac.

Fourthly, intrapericardial rupture is uncommon in these aneurysms. Rupture usually occurs into chambers of vessels in which the blood-pressure is less than in the aorta, resulting in an arteriovenous fistula (Schnitker, 1952).

Fifthly, the absence of an often associated ventricular septal defect. It has been suggested that congenital aneurysms of the right sinus of Valsalva are due to a defect in the fusion of the inferior septum with the aortic septum (Mall, 1912). However, Dilg (1883) found no aneurysms in this region, on examining 61 cases with ventricular septal defects.

Summary

A description is given of the direct intra-pericardial rupture of a congenital aneurysm of the right sinus of Valsalva, in a patient aged 72 years.

I wish to thank Dr. J. T. Prendiville for his help and encouragement; Dr. C. J. Gavey and Professor Pulvertaft (Westminster Hospital) for their advice on presenting the case; and Mr. H. Knight for the photograph.

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ANEURYSM OF AN ANOMALOUS RIGHT SUBCLAVIAN ARTERY

BY

W. C. D. RICHARDS AND C. E. ELLIOTT

From the Radcliffe Infirmary, Oxford

An anomalous right subclavian artery arising from the left side of the aortic arch distal to the left subclavian artery was first described by Hunauld (1735). In most cases the artery passes behind the œsophagus to reach the right side of the neck. The defect is usually attributed to a failure of development of the fourth right aortic arch, the caudal part of the right dorsal aorta persisting, sometimes with dilatation, to form the proximal part of the abnormal right subclavian artery. There are numerous accounts of this anomaly and they have been reviewed by Cairney (1925). Symptoms are unusual but in a small proportion of cases dysphagia is complained of. Bayford (1789) termed the difficulty in swallowing *dysphagia lusoria*.

Case Report

A lay brother in a religious order, aged 70 years, suddenly felt himself " choked by phlegm " and became so distressed that his friends thought he was about to die. When seen by his doctor shortly afterwards his general condition had improved but he was still breathing stertorously. A swelling of the neck, most marked above the right clavicle, was noted. On admission to hospital he was able to give the following story. For one year he had been short of breath when doing heavy work but had previously been in good health. Six weeks before he had noticed a painless swelling of the right side of his neck which had since been gradually increasing in size. He had experienced difficulty in swallowing, especially when eating solid foods, for about one month. During a recent cold he had noticed that " phlegm stuck in his throat."

On examination he was found to be a very fat man, breathing stertorously, but cheerful and not cyanosed. His neck was unusually thick and showed a diffuse doubtfully pulsatile swelling on both sides of the trachea. The posterior pharyngeal wall was firm and pushed forwards so that it almost touched the uvula. The temperature was 100° F., respiratory rate 24 a minute, pulse rate 90 a minute. The pulse was regular in rhythm but was weak at the right wrist. The femoral pulses were present and equal. The blood pressure was 150/90 mm. Hg in the right arm and 210/140 mm. Hg in the left arm. The heart was enlarged and loud systolic and diastolic murmurs were heard over the præcordium, the diastolic murmur being best heard over the third left costal interspace near the sternum. Minimal crepitations were heard over both lung bases. The vocal cords moved normally.

Investigations included: Hb. 15·3 g. per 100 ml.; white blood cells 7900 per c.mm.; Wassermann reaction and Kahn negative. Electrocardiogram: ischæmic heart disease and sinus tachycardia. X-ray examination (Dr. F. Kemp): " There is a large space-occupying lesion in the posterior mediastinum extending upwards into the neck anteriorly. The trachea is markedly displaced and narrowed." Barium swallow: " The œsophagus is displaced to the right with a deformity in the region of the aortic knuckle. The findings are compatible with a rupture of the aorta and extravasation of blood."

The diagnosis of a leaking aortic aneurysm was made. Treatment was essentially expectant in the hope that the aneurysm would seal. Penicillin to combat infection and sedatives to ensure rest were given. On the second day after admission a bluish discoloration of the chest due to subcutaneous extravasation of blood became visible, and this later spread downwards to the level of the nipples. His general condition improved slightly but on the fifth day after admission he suddenly became very dyspnœic and died a few hours later.

Necropsy. Externally, there was a diffuse swelling of both sides of the neck. The skin of the anterior surface of the chest showed bluish-yellow discoloration extending to the xiphisternum in the midline and to the level of the nipples elsewhere (Fig. 1).

The main finding on internal examination was an aneurysm of the first part of an aberrant right subclavian artery which had ruptured with resultant extravasation of blood into the tissues of the posterior

mediastinum and neck. Three arteries arose from the arch of the aorta; in place of the innominate artery there was a common carotid trunk which divided almost at its origin to form the right and left common carotid arteries; to the left of this bicarotid trunk the left subclavian artery arose in the usual way; just

FIG. 1.—Extravasation of blood into the subcutaneous tissues of the chest. Swelling of the neck prominent on the right side.

distal to the left subclavian artery the anomalous right subclavian was given off from the posterior aspect of the aortic arch (Fig. 2). This artery passed laterally and upwards to the right behind the œsophagus to gain its normal position in the root of the neck, and the right vertebral artery arose from it. At its origin the aberrant vessel was 3·5 cm. in diameter and there was aneurysmal dilatation of its first 6 cm., the maximum diameter being 4 cm. The inner surface of the aneurysm showed gross atheroma with much adherent old and recent blood clot which almost occluded the lumen. In many places the aneurysm wall was extremely friable and on its superior surface there was an ill-defined rupture. A massive hæmatoma in the posterior mediastinum extended to the base of the skull and displaced the posterior pharyngeal wall forwards so that it was touching the base of the tongue. The œsophagus and the trachea were compressed and the œsophagus was displaced sharply to the right (Fig. 3). Extravasation of blood into the muscles, connective tissue, and subcutaneous tissues of the neck had occurred.

The aorta and the coronary, iliac, and femoral arteries all showed severe atheroma. There was left ventricular myocardial hypertrophy and fibrosis. The liver was enlarged. Other findings were pulmonary œdema, a Meckel's diverticulum, an umbilical hernia containing omentum, and a right hydrocele.

Microscopical examination of sections taken from the aneurysm wall confirmed its atheromatous nature. Near the site of the rupture there was much fibrinous thrombus on the thickened and ulcerated intima. The medial wall was necrotic or consisted of fibrous tissue and organizing blood clot in which a few isolated fragments of elastic tissue remained. The adjacent mediastinal tissues contained organizing blood clot.

Comment

Dysphagia was a symptom in the fatal cases of aberrant right subclavian artery described by Bayford (1789) and by Kellock and Batten (1895). Kirby (1818) described a case in which death was due to perforation of the abnormal artery by a bone which had been swallowed. Holzapfel (1899) considered that *dysphagia lusoria* was only to be expected when there was aneurysmal dilatation of the first part of the aberrant artery; Gross (1946), however, mentions that dysphagia in infants might be due to stretching of the artery to form a taut band across the œsophagus, and that in later life arteriosclerotic changes might cause symptoms. In the case reported it is probable that the aneurysm had been present for some time. Dysphagia was complained of only when leakage of blood had produced a mediastinal hæmatoma. The collapse before admission was apparently the result of a rupture of the aneurysm which became partially sealed, only to break down again just before death. Even had the condition been correctly diagnosed during life it is

FIG. 2.—Lateral view of the arch of the aorta to show the orifice of the abnormal right subclavian artery. The orifices of the bicarotid trunk and the left subclavian artery are indicated by black rods.

FIG. 3.—Right antero-lateral view to show the common carotid arteries. The course of the right subclavian artery is marked by a black rod (white arrow) and the displacement of the œsophagus is indicated by the black arrow.

unlikely that treatment would have been successful. An abnormal right subclavian artery should, however, be remembered as a rare cause of dysphagia, particularly as radiological diagnosis during life can be made and in children surgical treatment is possible (Gross, 1946; Gross and Neuhauser, 1951).

Summary

An unusual case in which rupture of an aneurysm of an anomalous right subclavian artery was associated with neck swelling, *dysphagia lusoria*, and subcutaneous extravasation of blood, is described.

We wish to thank Professor L. J. Witts and Dr. A. H. T. Robb-Smith for permission to publish this case, also Mr. M. Morris for the photographs.

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SECOND EUROPEAN CONGRESS OF CARDIOLOGY

The Second European Congress of Cardiology has come and gone, but will remain in our memories, recalling the kindness and hospitality of our hosts and the beauty of Stockholm. In many directions it set a standard of organization that will be hard to better. It was so superb that it is difficult to single out any one thing for special praise, but some must be mentioned—the information bureau where ladies helped us in so many languages, the fine concert hall with such convenient arrangements, the efficient lanterns, and the excellence of the simultaneous translations into English, French, and German. On one occasion the writer noticed a minor error in the translation of a technical term and when the same term recurred a few minutes later the translator realized that her version had not been perfect and corrected it.

More than thirty countries were represented at the Congress. There were large delegations from Belgium, Denmark, France, Germany, Great Britain, Holland, Italy, Norway, Spain, Sweden, and the United States of America, and the Congress was pleased to see representatives from Czechoslovakia, Hungary, Poland, and Russia. An Englishman should feel humbled by the number of members who spoke so well in English.

It is evident that these Congresses attract large numbers and it is not easy for a city to house a thousand extra visitors. Most of us were housed with convenience and great comfort but some were rather far away, and clearly this had been one of the most difficult problems for the organizers.

The Congress was opened by the Minister of Education and Ecclesiastical Affairs, Mr. Ivar Persson, who was followed by Prof. Nylin, Sir John Parkinson, Prof. Mouquin, Prof. Weber, Dr. Paul White, and Prof. Chavez, all of whom addressed the Congress.

The scientific sessions went smoothly and easily so that it seemed a short time from the President's inaugural talk on the size of the heart on Monday to Friday's panel on the treatment of essential hypertension, when representatives of seven countries took part. Though great care had been taken in the arrangement of the simultaneous sessions, it was not possible for everyone to hear all the papers he would have wished. The organizers will have to continue to be ruthless—perhaps even more ruthless—in selecting the papers that can be read. It would be invidious to pick out any one paper. Perhaps the symposia were not always as successful as was hoped, and it seems that grouping three papers on related subjects where the authors read their communications at some length does not succeed in producing a general discussion on the subject: indeed, the chairman often found there was no time left for this. This applied to some of the round table conferences and panel discussions; one gained the impression that a great deal depended on the chairman asserting himself before and during the meeting to make the panel a real discussion rather than a sequence of individual papers.

The papers and discussions covered a very wide field and it is hard to say that any one subject occupied a predominant position. Hypothermia had passed from the experimental stage discussed at the Congress in London in 1952 to practical medicine, and pulmonary hypertension was discussed at some length. The treatment of cardiac infarction with anticoagulants was discussed less than it was two years ago and this was also true of the surgery of mitral disease and of congenital heart disease, except for septal defects. If we did not learn much that was new about the ætiology of coronary disease, we heard many useful papers on other common conditions and on the treatment of hypertension and of arrhythmias with quinidine.

The Congress booklets were at once available; they were perfectly produced and in a convenient form. The set comprised (1) the speeches at the opening ceremony, (2) the programme and list

Paul White
President
World
Congress
1954

John Parkinson
President
European
Congress
1952

Gustav Nylin
President
European
Congress
1956

of members, and (3) the abstracts of papers containing summaries of all the accepted communications. These were most helpful and will prove a valuable record of the scientific contributions to this successful congress.

The scientific exhibitions were outstanding, and the writer felt he had to miss one afternoon session so that he could see some of them adequately. They were clear and well arranged and could serve as models. Everyone was impressed by the fine angiocardiograms displayed so clearly, but each visitor would probably pick out different exhibits that had pleased him particularly. The writer, with diffidence when all were so good, mentions two exhibits from Malmö, one on the carcinoid syndrome and one on the natural history of rheumatic heart disease, also some diagrams and specimens of congenital heart disease shown by Snellen and others, and Condorelli's exhibit on diagnostic pneumomediastinum.

The setting for the Congress was almost ideal, the reception at the National museum where we had the pleasure of seeing the beautiful portrait of William Withering by the Swedish artist Von Breda; the perfection of the eighteenth-century Court Theatre at Drottningholm; the banquet in the magnificent Stadshuset; and finally the visit to the beautiful old university town of Upsala where we saw the castle and the cathedral and Rudbeck's anatomical theatre built in 1662, which reminded us how much these early theatres have influenced modern lecture theatres.

The pre-congress tour to the Arctic Circle was an enjoyable experience and no doubt the other tours after the Congress were as popular. It seemed that Paul White's advice on the importance of exercise for avoiding the onset and progress of coronary heart disease had been taken to heart by many cardiologists.

At the General Assembly, Evan Bedford was elected President of the European Society of Cardiology and Gustav Nylin was elected an Honorary President to join Professor Laubry and Sir John Parkinson. Lenègre and Condorelli were elected Vice-Presidents. François van Dooren and Ivan Mahaim were asked to continue as Secretary and Treasurer respectively. It was decided that the Third European Congress should be held at Rome in 1960, probably in September. The Third World Congress will be held in Brussels from September 14 to 21, 1958.

Everyone will wish to express their warmest thanks for the immense amount of trouble that must have been taken to produce such success, especially to Gustav Nylin our President and President of the Congress, to Edgar Mannheimer the Chairman of the Organizing Committee, to Karl Grewin the Secretary-General, to Lars Werkö Chairman of the Programme Committee, to B. Jonsson Chairman of the Exhibition Committee, to Mrs. Nylin and her committee for the excellent programme for the ladies, and to many others.

The Société Belge de Cardiologie have generously offered a prize of 100,000 Belgian francs for an essay on any cardiological subject to be awarded at the Third World Congress of Cardiology in 1958. Publications dealing with diagnosis, prophylaxis, or treatment will be particularly appreciated. The author may be of any nationality and must be under 50: the paper must be written in English or French and must not exceed 50 pp. quarto size, typewritten in double spacing, with no more than 10 illustrations (70 sq. cm. in size) and should be sent to the Secretary of the Board before May 1, 1958. Members may obtain further information from the Secretary, British Cardiac Society.

The Harvey Tercentenary Congress will be celebrated in London at the Royal College of Surgeons from June 3–8, 1957. In connection with this, a special all day meeting of the British Cardiac Society will be held on Thursday, June 6, at the Royal College of Surgeons: this will, of course, be open to members of the British Cardiac Society as usual. Those wishing to attend other parts of the Harveian Congress should write for information to the Secretary, The Harveian Society of London, 11, Chandos Street, W. 1.

The Annual General Meeting of the British Cardiac Society will be held as usual, on May 16, 1957, in Edinburgh.

ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

Increased Cerebrospinal Fluid Pressure and Papilledema in Malignant Hypertension. R. D. TAYLOR, A. C. CORCORAN, and I. H. PAGE. *Arch. intern. Med.*, **93**, 818–824, June, 1954.

The cause of papillœdema in hypertension is uncertain. It has been suggested that the level of the diastolic blood pressure is responsible, but this explanation is not universally accepted. The present authors measured the cerebrospinal fluid pressure (C.S.F.P.) in 200 hypertensive patients; 100 (49 men and 51 women, aged 19 to 65, average age 43) had hypertension without papillœdema and 100 (66 men and 34 women, aged 12 to 67, average age 43) had malignant hypertension with papillœdema.

The results were as follows. There was no relation between the level of the diastolic pressure and the C.S.F.P. in the 100 patients without papillœdema. In the 100 patients with papillœdema there was some relation statistically between the two, but not a close one, and there were many discrepancies—for example, 57 patients had a normal C.S.F.P.; of 16 patients with a C.S.F.P. exceeding 350 mm. H_2O, 14 had papillœdema and 2 had normal optic discs.

The authors conclude that there is no evidence of a causal relationship between papillœdema and the level of the diastolic blood pressure. *Arthur Willcox*

Treatment of Stokes–Adams Disease by External Electric Stimulation of the Heart. P. M. ZOLL, A. J. LINENTHAL, and L. R. NORMAN. *Circulation (N.Y.)*, **9**, 482–493, April, 1954.

The authors, working at Harvard Medical School and Beth Israel Hospital, Boston, report the results of their use of an electrical stimulator (briefly described) placed over the præcordium in 14 cases of Stokes–Adams disease. The stimulus from the artificial pacemaker could be varied in strength and frequency, and was designed to overcome periods of extreme ventricular bradycardia or standstill in cases of complete auriculo-ventricular block. Electrocardiograms demonstrated the effectiveness of this external electrical stimulator in 13 of the 14 patients. Detailed cardiac histories are given of the 14 patients, of whom 10 eventually died, 8 from a Stokes–Adams attack.

Syncope due to ventricular standstill was terminated immediately. An effective circulation was maintained for periods of up to 4 days with continuous stimulation. In most cases idioventricular rhythm returned after withdrawal of the artificial stimulation, and one patient has had no further syncopal attacks for a year. The stimulator proved ineffective in ending attacks of persistent ventricular tachycardia, which proved fatal in 3 cases; it did, however, prevent the recurrence of such attacks during its application for ventricular standstill. *D. W. Barritt*

Endocardial Fibroelastosis: a Factor in Heart Disease of Obscure Etiology. A Study of 20 Autopsied Cases in Children and Adults. W. A. THOMAS, R. V. RANDALL, E. F. BLAND, and B. CASTLEMAN. *New Engl. J. Med.*, **251**, 327–338.

The authors, reviewing the post-mortem reports of all cases of heart disease of obscure ætiology out of 10,000 cases coming to necropsy at the Massachusetts General Hospital in the past 25 years, have differentiated a group of 20 cases of chronic heart disease with hypertrophy of uncertain ætiology and extensive fibroelastic thickening of endocardium and subendocardium. These they divided arbitrarily into three subgroups: infantile, childhood (2 to 16 years), and adult cases.

In the 4 infantile cases the patient had had symptoms for some months before death. There was marked cardiac hypertrophy with endocardial fibroelastosis overlying a relatively normal myocardium, but no evidence of any inflammation or thrombosis. The authors postulate that in these cases the ætiology was congenital. In the childhood group, also of 4 cases, the findings were similar except for later onset of symptoms and slighter degree of hypertrophy, and it is considered that these also were congenital in origin.

The 12 adult cases were morphologically similar to the other types of case, but in 9 of them mural thrombi were present. There was no gross myocardial fibrosis or evidence of inflammation. The history was longer than in the younger groups, congestive failure was prominent, and some patients had a family history of obscure heart disease. The authors discuss the ætiology of this type of heart disease and conclude that despite the lack of specificity of the fibroelastosis and the late onset of symptoms, it too is congenital in origin. The relationship between the pathological changes and symptoms is also discussed and comparisons are made with other obscure heart diseases. *D. Goldman*

Control of Blood-pressure by Combined Action of Reserpine and Pentapyrrolidinium. F. H. SMIRK, A. E. DOYLE, and E. G. MCQUEEN. *Lancet*, **2**, 159–162, July 24, 1954.

The authors describe the results of the treatment of 37 hypertensive patients with a combination of reserpine, an alkaloid from *Rauwolfia serpentina*, and pentapyrrolidinium, a methonium compound, both given by mouth. Reserpine was given first, up to a maximum dose of 0·5 mg. thrice daily, the aim being to give the highest dose which the patient could tolerate without discomfort. Pentapyrrolidinium was given in an initial dose of 20 mg. repeated after 12 hours, and then increased by 20-mg. increments according to the reactions of the patient until a maintenance dose ranging from 60 to 700 mg. twice daily was reached. As an emergency measure, for example in cases of hypertensive heart

failure or malignant hypertension, the drugs were given simultaneously.

It was found that, as compared with pentapyrrolidinium alone, the combined therapy allowed the blood pressure to be stabilized at a lower level and with less fluctuation, and the side effects, such as dryness of mouth, constipation, and postural faintness, were diminished. It has been the authors' experience that treatment with blood-pressure-reducing agents reduces the incidence of hypertensive heart failure and lessens the need for digitalis and mersalyl. However, cerebral vascular accidents are still frequent, and many of these appear to be due to sudden rises in blood pressure, especially following unauthorized interruption of drug treatment.

K. G. Lowe

La Valvola Mitrale. M. A. CHIECHI and C. P. BAILEY, Rome: Il Pensiero Scientifico, 1955. Pp. 531. Bibliography. 38 plates. Price 5000 lire.

This book is based on the findings in 753 patients with mitral valve disease, most of whom were submitted to surgery. The anatomy of normal and abnormal mitral valves has been studied in detail by Chiechi. In particular, attention is drawn to small intermediate cusps which are frequently present between the main leaflets. The posterior intermediate cusp was absent in 37 per cent of normals, and this may have some bearing on the occurrence of mitral incompetence. Other factors considered to favour incompetence are irregular distribution of scarring in the valve and the downward dislocation of the posterior cusp which results from atrophy of the inflow tract of the left ventricle.

The section on clinical diagnosis is very brief and not up to the standard of the rest of the book. Correlation of preoperative assessment with operative findings was closest (89%) in cases considered to have pure stenosis; when co-existent incompetence was diagnosed operative confirmation was obtained in only 45 per cent.

One somewhat unusual view expressed is that patients who exhibit less than a 20 per cent rise in pulmonary " capillary " pressure are unsuitable because of irreversible changes in the pulmonary vascular bed. Operative technique is described in great detail. Of 291 cases followed subsequently for from one to five years, the results were regarded as excellent in 54 per cent and satisfactory in 36 per cent.

This book is detailed and largely accurate, clearly written and well illustrated. It would be improved by the provision of a proper index and by correction of errors in spelling and dates in the bibliography.

D. Weitzman

Inositol and Mannitol Hexanitrates in Hypertension Management. L. M. BERNSTEIN and A. C. IVY. *Circulation* (*N.Y.*), **12**, 353–360, Sept., 1955.

The effects of inositol hexanitrate (10-mg. tablets), of mannitol hexanitrate (30-mg. tablets), and of a placebo in lowering the blood pressure were compared in 32 ambulatory out-patients with hypertension, the average blood pressure being 197/111 mm. Hg. The various tablets, which were of identical appearance, were given for 2-week periods in rotation and the blood pressure was measured at the end of each period. The dose of the drugs was increased as the trial proceeded by increasing the number of tablets. Small doses of the hexanitrates (4 to 6 tablets 4 times a day) were without effect, but larger doses (9 to 12 tablets 4 times a day) resulted in small (up to 8 mm. Hg) but statistically significant falls in the systolic and diastolic blood pressures. The authors attribute the absence of effect of the small doses of the hexanitrates to the development of tolerance, and additional studies on 15 patients showed that tolerance developed in 8 days on the average and was lost within 10 days of discontinuing the drugs. They suggest that these findings should be borne in mind when evaluating or using organic hexanitrates in the management of hypertension, and that it is important to adjust the dose to the tolerance of the individual patient.

W. J. H. Butterfield

Molar Sodium Lactate. Its Effect in Complete Atrioventricular Heart Block and Cardiac Arrest Occurring during Stokes–Adams Seizures and in the Terminal State. S. BELLET, F. WASSERMAN, and J. I. BRODY. *New Engl. J. Med.*, **253**, 891–900, Nov. 24, 1955.

The authors now present a further report, illustrated with case histories, on the effect of a molar solution of sodium lactate upon the ventricular rate and conduction in patients with various types of heart block. In total heart block 120 to 150 ml. of molar sodium lactate given intravenously over the course of 10 to 15 minutes produced an increase in pulse rate by some 5 to 10 beats per minute in 10 out of 12 cases. The electrocardiogram occasionally showed ventricular extrasystoles while the infusion was being given, or transient changes in QRS configuration and prolongation of S–T as in alkalosis. The effect on the pulse rate passed off in an hour or two; a more sustained effect could be achieved, however, by the oral administration of 90 ml. of the solution every 4 hours.

In cases of hyperkalæmia with bradycardia, intraventricular conduction defect, bouts of ventricular fibrillation, and hypotension lactate solution appeared to act immediately in suppressing the arrhythmia and improving ventricular conduction and rate, and the serum potassium level also fell. Similar beneficial effects were noted in the suppression of Stokes–Adams attacks (3 cases) associated with frequent periods of ventricular asystole or fibrillation. In 12 cases of terminal cardiac arrest with disturbances of ventricular conduction and rhythm the heart beat was restored in a few, though only temporarily.

J. A. Cosh

The Results of Valvotomy for Aortic Stenosis. C. G. BAKER and M. CAMPBELL. *Lancet*, **1**, 171–175, Jan. 28, 1956.

The operation of aortic valvotomy carries with it the danger of producing incompetence if a calcified and deformed valve is split. This danger should not be so great in the case of congenital stenosis. In this paper the authors discuss the results obtained at Guy's Hospital, London, in 16 patients who had predominant aortic stenosis sometimes with slight incompetence.

The patients' average age was 46, though 2 were children with congenital stenosis. The predominant symptoms were syncopal attacks and anginal pain, both of which occurred in many cases. The size of the heart was not abnormally great and the electrocardiogram showed evidence of marked left ventricular strain. Dyspnœa and cardiac asthma in some cases suggested left ventricular failure.

There were 6 operative deaths. Of the survivors, 5 were greatly improved as a result of the operation and a further 5 obtained some benefit, but 2 of these died at a later date. These results in cases of pure aortic stenosis are not so satisfactory as those obtained in cases of associated mitral and aortic disease. But it is noted that many of the patients were operated on at a late stage of their disease. *T. Holmes Sellors*

Left Axis Deviation in Tricuspid Atresia and Single Ventricle. The Electrocardiogram in 36 Autopsied Cases. C. A. NEILL and A. J. BRINK. *Circulation (N.Y.)*, **12**, 612–619, Oct., 1955.

In this further communication from the Johns Hopkins Hospital, Baltimore, the electrocardiographic and necropsy findings in 28 selected cases of tricuspid atresia and 8 of single ventricle with left axis deviation are analysed.

Evidence of left axis deviation was present in 24 of the cases of tricuspid atresia, while in 20 of the 21 cases in which tracings from præcordial leads were taken they showed signs of left ventricular preponderance. Tracings from these leads were available in 7 cases of single ventricle, in 3 of which there were large equiphasic QRS complexes in V1 to V5, while one showed right ventricular preponderance; left ventricular preponderance was found in the remaining three.

Electrocardiographic evidence of right atrial hypertrophy was present in 23 cases of tricuspid atresia and in 4 of single ventricle. In tricuspid atresia, but not in single ventricle, a correlation was found between the form of the P wave and the size of the interatrial communication as revealed at necropsy. *T. Semple*

Patent Ductus Arteriosus with Pulmonary Hypertension. I. M. ANDERSON and H. M. T. COLES. *Thorax*, **10**, 338–347, Dec., 1955.

The authors review the cases of 9 children aged 1 to 6 years who were diagnosed clinically at the Westminster Hospital, London, as having a patent ductus arteriosus with pulmonary hypertension. Catheterization was repeated after ligation of the ductus in 6 cases, in all of which the pulmonary arterial pressure was found to be normal.

With the exception of one child who died 4 weeks after operation, all the patients showed striking clinical improvement. The child who died was shown to have had a reversed shunt through the ductus, and at necropsy a severe degree of atherosclerosis in the smaller pulmonary vessels and gross hypertrophy of the main pulmonary trunk were found. There was associated stenosis of the aortic and mitral valves. The authors consider that cardiac catheterization is indicated whenever well-marked pulmonary arterial dilatation, enlargement of both ventricles, and increased pulsation of the smaller pulmonary vessels are found on fluoroscopy in a child with the clinical features mentioned above. A precise diagnosis made in this way will enable operative treatment of the ductus to be carried out before irreversible changes occur. *A. M. Macarthur*

Patent Ductus Arteriosus with Pulmonary Hypertension. An Analysis of Cases Treated Surgically. F. H. ELLIS, J. W. KIRKLIN, J. A. CALLAHAN, and E. H. WOOD. *J. thorac. Surg.*, **31**, 268–285, March, 1956.

Since there is a good deal of uncertainty regarding the selection for surgical treatment of patients with patent ductus arteriosus (P.D.A.) associated with pulmonary hypertension, a total of 72 reported cases of P.D.A. with pulmonary hypertension were first reviewed. In this series operative closure of the ductus carried an over-all mortality of 18 per cent (13 deaths), but in the 16 patients with a right-to-left shunt the rate was 56 per cent (9 deaths).

The authors then consider in some detail 30 out of 272 cases of P.D.A. operated on at the Mayo Clinic up to April, 1955, in which cardiac catheterization before operation showed a pulmonary arterial pressure higher than 60 mm. Hg. The ages of the patients ranged from 2 months to 59 years, but half of them were under 15 years. A right-to-left shunt was demonstrated in 14 cases, but had undoubtedly been present at some time in several others. Of the 30 patients, 5 died as a result of operation (mortality 17%) and there were 2 later deaths; all the deaths occurred in patients with a right-to-left shunt, representing a mortality of 50 per cent in this type of case. Of the 23 survivors, 20 are well. Recanalization occurred in 3 patients, 2 of whom are well, and one is included in the late deaths. A satisfactory reduction in pulmonary arterial pressure was noted in 9 out of 12 patients in whom closure of the ductus was successful, as shown by re-catheterization in the postoperative period. This satisfactory response included 3 cases in which a right-to-left shunt had been demonstrated before operation.

The authors conclude that all cases of P.D.A. with left-to-right shunt should be treated by operation, but that closure should not be carried out in those with a predominantly right-to-left shunt, or in those in whom the pulmonary arterial pressure rises and the systemic pressure falls when the ductus is occluded on the operating table. Patients with P.D.A. resulting in pulmonary hypertension usually have a short wide ductus; the ligation of such a ductus is unsatisfactory, the recurrence rate being high, and division is the only method to ensure success. *F. J. Sambrook Gowar*

The Surgery of Patent Ductus Arteriosus. A Report of the Section on Cardiovascular Surgery. D. H. WATERMAN, P. C. SAMSON, and C. P. BAILEY. *Dis. Chest*, **29**, 102–108, Jan., 1956.

At the request of the American College of Chest Physicians the authors have collected and analysed the results of 3896 operations for patent ductus arteriosus performed by 49 surgeons in various parts of the United States and abroad. Of the patients concerned, 2929

were children and 967 were adults. Of the former, 69 per cent were symptom-free before operation, 27 per cent showed signs of myocardial insufficiency, and infection was present in 4 per cent, whereas only 48 per cent of the adults were symptomless, 41 per cent having myocardial insufficiency and 11 per cent being infected. The operative mortality in the younger group was 2·3 per cent and in the adult group 5·5 per cent.

Nearly 60 per cent of the surgeons practised division of the ductus, as opposed to ligation. The initial mortality rates were practically identical for both types of operation in both children and adults. The majority of the collaborating surgeons favoured ductal interruption in the presence of pulmonary hypertension up to a pressure of 90 mm. Hg systolic. For patients in whom there was reversal of the shunt almost all the surgeons considered that operation should not be advised, but a small minority (8) were prepared to explore and determine the effect of temporary occlusion of the duct; if this resulted in a fall in pulmonary arterial pressure, then they considered that the duct should be permanently interrupted, but not otherwise.

A rather surprising finding was the incidence of aneurysms, which among 1043 cases reported by 17 surgeons was as follows: 8 of the ductus, 35 of the pulmonary artery, and 31 of the aorta—an over-all incidence of 7 per cent.

[It is to be regretted that the authors make no mention of recanalization, particularly in relation to the question of ligation or division, since it was on this score that surgical division as opposed to ligation was originally recommended.] *W. P. Cleland*

Ventricular Septal Defects with Pulmonary Hypertension. J. W. DuSHANE, J. W. KIRKLIN, R. T. PATRICK, D. E. DONALD, H. R. TERRY, H. B. BURCHELL, and E. H. WOOD. *J. Amer. med. Ass.*, **160**, 950–953, March 17, 1956.

The authors report from the Mayo Clinic the results in 20 cases of ventricular septal defect in 3 of which the defect was closed by direct suture and in 17 by insertion, at open cardiotomy, of a non-absorbable polyvinyl sponge prosthesis. Preoperative cardiac catheterization indicated large arterio-venous shunts and, in most cases, pulmonary arterial pressures close to the systemic arterial pressure.

There were 4 postoperative deaths, 3 being among the first 7 cases but only one among the next 13; the cause of death was pulmonary complications, associated in one case with complete atrio-ventricular dissociation. Interference with the conduction mechanism occurred in 9 cases, 6 showing right bundle-branch block. The presence of left ventricular hypertrophy as well as right ventricular hypertrophy gave a more favourable prognosis. The 16 survivors have improved, with loss of the arterio-venous shunt. *J. Robertson Sinton*

Direct-vision Suture of Interatrial Septal Defect during Hypothermia. H. SWAN, S. G. BLOUNT, and R. W. VIRTUE. *Surgery*, **38**, 858–871, Nov., 1955.

This article from the University of Colorado School of Medicine, Denver, is concerned with the surgical treatment of atrial septal defects, and provides a review of the authors' opinions concerning the various methods of closure available and of their experience with suture under direct vision with hypothermia in 29 cases.

Of the 29 patients operated upon, 3 had pure septum primum lesions, 21 pure septum secundum lesions, and 5 had multiple defects; 14 were less than 15 years old and 6 were over 30. Pulmonary vascular resistance did not appear to be related to age, although the size of the heart was greatly enlarged in all those over 30 years of age. Six of the patients have died, including 2 of the 3 with septum primum defects. Postoperative cardiac catheterization was carried out on 21 of the survivors and indicated complete closure in all but 2 instances. Of the 6 deats, 3 were due to ventricular fibrillation, one to hæmorrhage, and the remaining 2 to progressive thrombosis of the pulmonary arteries. Only 3 of the deaths could be in any way attributed to hypothermia, and 2 of these occurred in cases of the septum-primum type.

These results are very encouraging, and suggest that hypothermia provides an effective and practicable method of dealing with the problem of the closure of atrial septal defects. *W. P. Cleland*

A Controlled Study of the Effect of Intermittent Heparin Therapy on the Course of Human Coronary Atherosclerosis. H. ENGLEBERG, R. KUHN, and M. STEINMAN. *Circulation* (*N.Y.*), **13**, 489–498, April, 1956.

The effect of prolonged, intermittent administration of heparin in patients who had had an attack of myocardial infarction more than 3 months before was studied at the Cedars of Lebanon Hospital, Los Angeles. Over 200 such patients were divided into two comparable groups, one of which received 200 mg. of concentrated aqueous solution of heparin subcutaneously twice a week, and one was given isotonic saline injections in a similar manner. The progress of the underlying atherosclerotic process was assessed from such factors as death from cardiovascular disease, recurrence of cardiac infarction, gangrene of a limb necessitating amputation, and cerebral vascular accidents, excluding those occurring during the first month of treatment.

Over a period of 2 years there were 18 non-fatal recurrences and 21 deaths from cardiovascular disease in the control group, compared with 5 non-fatal recurrences and 4 deaths from heart disease in the heparin-treated group, the difference being statistically significant ($p = <0{\cdot}01$). Symptomatic improvement was also noted in the heparin-treated group. In the course of over 17,000 injections of heparin there were only 3 instances of major hæmorrhage.

Lipoprotein values were determined in a few cases only, but from these it appears that in a minority of patients there is a sustained reduction in the average level of low density lipoproteins, while in the majority there is only a temporary decrease following each injection. The results were considered to depend on this effect and on the physiological role of heparin in the serum transport phase of fat metabolism rather than on intermittent anticoagulation. *R. S. Stevens*

Total Anomalous Pulmonary Return. An Analysis of Thirty Cases. V. L. GOTT, R. G. LESTER, C. W. LILLEHEI, and R. L. VARCO. *Circulation (N.Y.)*, **13**, 543–552, April, 1956.

The authors present a detailed analysis of 30 cases of total anomalous pulmonary venous return to the heart in infants. In 23 cases the diagnosis was confirmed at necropsy, in 3 at operation, and in 4 cases it was accepted after thorough clinical evaluation; 17 patients were male and 13 female. Of the 23 cases examined post mortem, 13 were found to have associated patent foramen ovale, 4 patent foramen ovale together with patent ductus arteriosus, and 6 had multiple major defects. Most of the patients failed to survive the first 3 months of life, but the 7 still living are all past infancy and one is a 33-year-old woman with two children.

Pulmonary venous drainage was into the left innominate vein and thence to a right superior vena cava (a route mistakenly called "persistent left superior vena cava" by some authors) in 7 cases, into the coronary sinus in 4, into the right atrium in 4, the inferior vena cava in 2, the right superior vena cava in 2, and into the portal vein, the coronary sinus and left innominate vein, the inferior vena cava and left innominate vein, the abdominal visceral veins, and the anterior cardinal veins in one case each; in 2 cases the route of drainage was not fully demonstrated. Cardiac catheterization, performed in 13 cases, showed the striking feature of high oxygen saturation in the right atrium, this being equal to or higher than that in the systemic arterial blood. Pulmonary hypertension was common, as was also electrocardiographic evidence of right ventricular hypertrophy; only one patient had right bundle-branch block. On radiological examination only 3 cases showed the well-known "figure-of-eight" appearance formed by the engorged superior vena cava and the heart; in the postero-anterior position 12 showed a square-shaped heart due to massive enlargement of right atrium and right ventricle, which the authors believe to be characteristic. There was increased pulmonary vascularity, which became very marked after the first few months of infancy. Of the 6 patients subjected to surgery, 3 survived partial or totally corrective procedures. *K. G. Lowe*

Direct Vision Intracardiac Surgery in Man Using a Simple, Disposable Artificial Oxygenator. C. W. LILLEHEI, R. A. DEWALL, R. C. READ, H. E. WARDEN, and R. L. VARCO. *Dis. Chest*, **29**, 1–8, Jan., 1956.

The authors describe in simple terms the "bubble oxygenator" which they have developed and used clinically at the Heart Hospital (University of Minnesota), Minneapolis, whereby the patient's blood is efficiently oxygenated extracorporeally. They state that their former cross-circulation technique for open operations on the heart has now been replaced entirely by the new oxygenator. In essence the apparatus (which is clearly illustrated in a photograph) consists of a length of wide-bore plastic tubing in the shape of an inverted U through which blood is slowly pumped, while 100 per cent oxygen is introduced directly into the moving column through a series of hypodermic needles. Frothing is largely eliminated by contact with a potent, non-toxic, silicone anti-foaming agent. As the blood descends to a settling tube on the distal side bubbles of excess oxygen, together with carbon dioxide, rise to the surface and escape. The apparatus is simple and easily replaceable, and it is claimed that contact with the plastic does not damage the blood cells or affect the clotting mechanism as is the case with glass. The patients are given heparin in doses of 1·5 mg. per kg. body weight, and all replacement blood is similarly heparinized. A rate of flow varying from 172 to 600 ml. per minute was obtained in the cases described.

Details are given of 7 patients, all children, on whom open cardiac operation for septal defect was carried out. In these patients the length of time the heart was open varied from 8½ to 18 minutes. In an addendum the authors state that 36 patients aged from 16 weeks to 21 years have since been operated on with the aid of the oxygenator, the maximum "by-pass" time in this group being 50 minutes. *W. P. Cleland*

De-epicardialization: a Simple, Effective Surgical Treatment for Angina Pectoris. D. E. HARKEN, H. BLACK, J. F. DICKSON, and H. E. WILSON. *Circulation (N.Y.)*, **12**, 955–962, Dec., 1955.

The authors review the various methods that have been suggested for the treatment of angina pectoris by increasing the vascular supply to the myocardium and the experimental work that has been done in this connexion. They point out that the degree of success achieved with each of these methods has been remarkably constant, and conclude that increase in the intrinsic coronary flow rather than the provision of an external collateral blood supply is the most important factor, whatever the operation.

Prompted by the work of Burchell, which suggested that the epicardium is the chief barrier to vascularization of the myocardium from extrinsic sources, they have carried out experiments on dogs, to determine the safest and most effective method of removing it. Finding that the application of 95 per cent phenol was satisfactory in that it destroyed the epicardium without increasing the irritability of the heart, they have now applied this finding to the clinical field in 18 cases of severe angina. There was no operative mortality, but 2 patients who had been relieved of pain died 2 months after operation from recurrent coronary infarction. In all but 2 of the remaining cases there was complete relief of pain. The authors consider that the results so far obtained justify the further application of this procedure for the relief of intractable anginal pain. *J. R. Belcher*

Staphylococcal Infection following Cardiac Surgery. H. A. FLEMING and R. M. E. SEAL. *Thorax*, **10**, 327–337, Dec., 1955.

The authors draw attention to the incidence of staphylococcal septicæmia and local staphylococcal infections following cardiac surgery and give clinical details of 9 such cases encountered at Sully Hospital, Glamorgan. In 7 the complication followed mitral valvotomy and in 2 ligation of a patent ductus arteriosus. In 3 of the cases the infection was due to the "non-pathogenic,"

coagulase-negative variety of staphylococcus. The diagnosis in the early stages may be difficult as this post-operative endocarditis does not produce the usual clinical picture. Five of these patients developed signs of pulmonary infarction which distracted attention from the underlying septicæmia. The 2 cases in which infection occurred after ligation of the ductus arteriosus were diagnosed by the occurrence of hæmoptysis and the appearance of a new radiographic shadow at the operation site owing to the development of a false aneurysm. The patient with a localized myocardial abscess, who died suddenly, was previously in apparently good health.

It is suggested that the development of this condition is due to the opportunity for infection provided by endocardial trauma. In a study of the staphylococcal population present in an operating theatre and its personnel during the performance of mitral valvotomy it was found that by the time the crucial point of the operation was reached all gloves, suture material, and packs were heavily contaminated. *A. M. Macarthur*

Basal Horizontal Lines on Chest Radiographs. Significance in Heart-disease. R. E. ROSSALL and A. J. GUNNING. *Lancet*, **1**, 604–606, May 5, 1956.

A study was undertaken at the General Infirmary at Leeds to discover whether any relationship existed between the occurrence of the short horizontal, peripheral basal lines seen on chest radiographs and either the left auricular or pulmonary arterial pressure. The series comprised 100 patients with mitral valve disease and 16 with pulmonary hypertension arising from other causes.

The authors conclude: (1) basal horizontal lines on the chest radiographs of patients with mitral disease are accompanied by a raised left atrial pressure; (2) lines invariably appear when the mean left atrial pressure exceeds 24 mm. Hg; and (3) elevation of the pulmonary arterial pressure alone appears to play little part in the production of lines. They further suggest that the factor responsible for the lines is a rise in pulmonary capillary venous pressure to a level exceeding the colloid osmotic pressure of the plasma proteins; this they regard as indirect evidence for the view that the anatomical basis of the lines is an increase in the bulk of the interalveolar septa. *Sydney J. Hinds*

The Long-term Use of the Oral Diuretic 3-Chloromercuri-2-methoxy-propylurea (Neohydrin) in Ambulatory Patients. J. M. EVANS and R. A. MASSUMI. *Ann. intern. Med.*, **44**, 124–132, Jan., 1956.

The authors report, from Washington, D.C., the results of a long-term clinical trial of the oral diuretic "neohydrin" on 40 patients, of whom 38 had congestive heart failure and 2 had chronic renal disease. Parenteral mercurial diuretics were successfully replaced by neohydrin (given in tablets each equivalent to 10 mg. of mercury) for periods of 8 to 84 weeks (average 38·6 weeks); effective maintenance doses ranged from 2 to 6 tablets a day.

Two patients, with poor oral hygiene, developed gingivitis. In 5 cases the diuretic control was unsatisfactory, and in 9 the drug had to be withdrawn because of side-effects (dermatitis, abdominal pain, bloody diarrhœa, and stomatitis) after periods ranging from 3 days to 29 weeks. The authors conclude that neohydrin is an effective and reasonably safe oral diuretic.

W. J. H. Butterfield

The Function and Structure of the Arteries as Related to Age. An Angio-chemical Study. G. HEVELKE. *Angiology*, **7**, 39–54, Feb., 1956.

The relationship between function and chemical composition of the arteries was studied at Leipzig University, 10-cm. lengths of the brachial and femoral arteries from 96 subjects being examined post mortem. The arteries showed a progressive increase in weight with age, the brachial artery doubling in weight from the third to the eighth decade while the weight of the femoral artery increased rather more. These increases occurred in spite of a fall in dry weight, attributed by the author to the accumulation of a water-rich mucoid substance. The calcium, cholesterol, and ash contents of the two arteries increased slowly until the fifth decade, after which the values for the femoral artery rose much more steeply than those for the brachial artery. For example, in the first decade of life the cholesterol content of the brachial artery per 100 g. wet weight was 126 mg. and of the femoral artery 124 mg.; in the fifth decade the figures were 217 and 246 mg., and in the eighth decade 256 and 648 mg.

The chemical composition of the right artery was compared with that of the left in 52 subjects. Up to the age of 40 years differences were insignificant, but between 40 and 80 years the right artery weighed more and contained more ash, cholesterol, and calcium than the left. In 52 diabetics aged 20 to 80 years there was an increase in all values. For example, between 20 and 40 years of age the right femoral artery in diabetics weighed twice as much and contained three times as much ash and cholesterol and six times as much calcium per unit wet weight as did the normal artery.

M. C. Berenbaum

Diagnosis and Treatment of Vascular Disorders (Angiology). Edited by Saul S. Samuels, London. Ballière, Tindall & Cox. 1956. £6 8*s*.

This book is written by a large number of contributors, and consists of a series of essays on various aspects of peripheral vascular disease; much useful information is given, including extensive bibliographies. In some of these, as in the material included in the text, there could perhaps have been better selection, and multiple authorship sometimes results in an unfortunate allocation of space to different subjects. Aortic and iliac obstruction deserve greater mention, also the clinical localization of the site of an arterial obstruction, which is now well established. The place of arterial grafting, in the treatment of occlusive arterial disease, must obviously be more fully considered in another edition. These are, however, minor criticisms of a valuable book, which embodies the opinions of various physicians and surgeons on widely different aspects of the subject. The illustrations, particularly the reproductions of arteriograms, are excellent. *Lawson McDonald*

THE SYNDROME OF THE SUSPENDED HEART

BY

WILLIAM EVANS AND H. G. LLOYD-THOMAS

From the Cardiac Department of the London Hospital

Received February 27, 1956

When the electrocardiogram of occasional patients in whom a description of pain in the chest did not tally with that customarily identified with cardiac pain was examined, the finding of S–T depression caused surprise and confused the diagnosis. In order to discover the reason for this cardiographic irregularity we assembled for special study 13 patients who possessed such an abnormal tracing which had been recorded in the recumbent position.

A peculiar stance of the heart within the thorax was found common to each case, and in this paper we describe circumstances, the recognition of which will prevent a wrong interpretation of the electrocardiogram obtained in a group of subjects with chest pain.

The Cases Described

Of the 13 patients, eight were men and five women. Their ages varied from 18 to 68 years; there were eight between 18 and 30, three between 30 and 60, and two over 65 years. All of them were of average height; eight were of slender physical build, four of medium build, and one was stout. Scoliosis was slight in one and moderately severe in another. None showed depression of the sternum and none had emphysema.

Chest pain was a presenting symptom in nine patients and in seven of these it was the only complaint; in the other two it was accompanied by palpitation in one and by loss of weight in the other. Three patients complained of palpitation only, but in none was this caused by paroxysmal tachycardia. The thirteenth was referred for examination as a possible case of mitral stenosis, but this could not be confirmed and the heart was judged to be healthy. In six of the nine patients with chest pain it was felt on the left side and usually below the breast. In the other three the pain was in the region of the right breast in one, behind the sternum in one, and across the chest in the third. The duration of the pain varied from momentary stabs to continuous pain that persisted for a whole week. In three the pain was described as sharp; in five it was an ache, and in one it was likened to a tight band round the chest. Deep inbreathing increased the pain in two, movement of the right arm induced it in one patient, while walking caused it occasionally in another.

Routine clinical examination failed to show evidence of cardiovascular disease in any of the 13 cases, and the blood pressure was never raised. A soft systolic murmur heard to the left of the sternum in two instances was considered to be innocent.

The Electrocardiogram. In each of the 13 cases the electrocardiogram (Fig. 1) showed a design that differed from the accepted normal tracing in a consistent way. Thus, the T wave was inverted and/or the S–T segment was depressed in lead II and to a greater extent in leads III and IIIR (lead III recorded during deep inspiration). The T was also low in CR7 in seven cases and the S–T segment depressed in another four; in only two was the curve natural in this lead. In two instances there was also depression of the S–T in CR4, and in one of them (Case 6), with severe scoliosis, this change was a noticeable feature.

The P wave was natural and if bifid it was never tall. The P–R segment was frequently depressed, particularly in leads that showed S–T depression. None showed pathological Q waves.

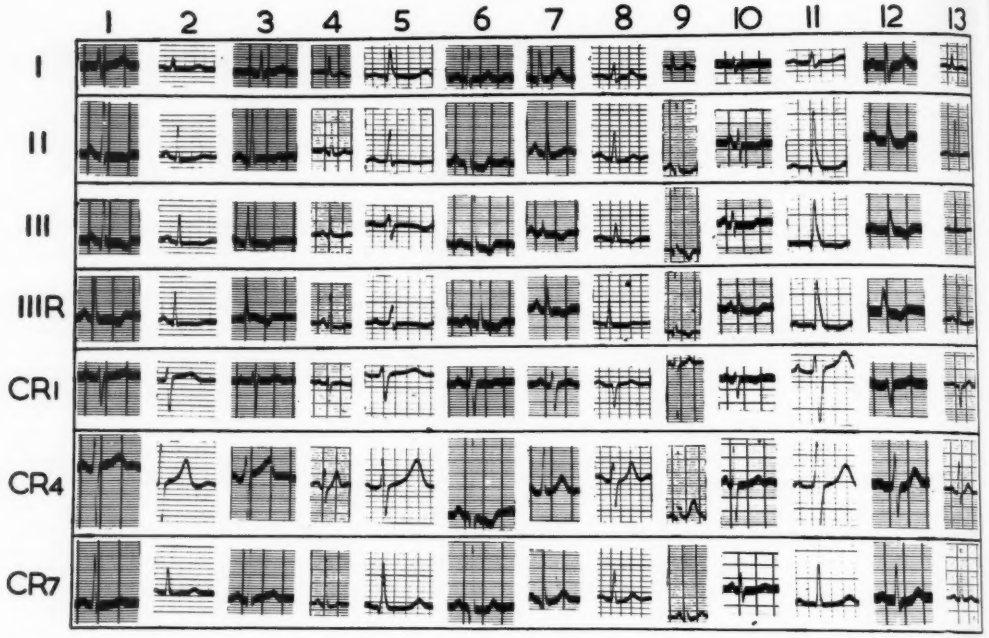

FIG. 1.—The electrocardiogram in 13 patients who showed the syndrome of the suspended heart. The figures above indicate the case numbers.

In lead I the voltage was rather low in seven cases. The R wave in limb leads was tallest in II and in 10 cases it was taller in III than in I. The S wave in CR1 was always larger than the R wave. In lead I, S was absent in five, small in six, and moderately deep in two: in CR7, S was absent in eight, and small in five cases. The unipolar limb leads supplied no added information. Thus, aVR and aVL were within normal limits, the S–T being depressed in aVF and aVFR (aVF recorded during deep inspiration). The vectorcardiogram when taken did not demonstrate the deformity as clearly as, nor help to explain its mechanism to better advantage than, did the orthodox electrocardiogram.

The tracing repeated after strenuous physical exercise did not show in a single instance any accentuation of the deformity, giving a so-called positive reaction. This test proved valuable in differentiating this innocent tracing from that obtained in cardiac infarction, so placed in the postero-inferior aspect of the heart, as to produce a comparable cardiogram. Thus, strenuous exercise accentuated the deformity in the pathological tracing, giving a positive reaction (Fig. 2).

Radiology of the Heart. The heart was never enlarged. Once it was displaced some distance to the left because of scoliosis. In the other cases it occupied a natural position in the *anterior* view, and during quiet respiration the customary cardiophrenic relationship appeared to be preserved. On deep inspiration, however, the heart and diaphragm parted to an unusual distance reducing the obtuseness of the left cardiophrenic angle, and on the right side uncovering the inferior vena cava. In the *left oblique* view the appearance was more arresting, so that the heart, lifted from its diaphragmatic platform, appeared to be suspended in mid-thorax from its vascular pedicle above, and anchored centrally by the inferior vena cava below. Similarly, in the *right oblique* view the cardio-diaphragmatic separation assumed a characteristic appearance with the slanting course

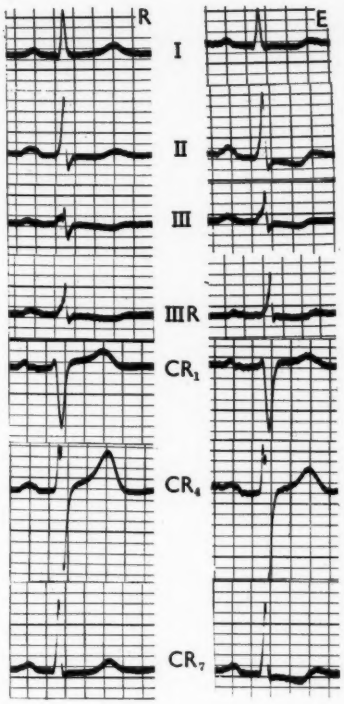

FIG. 2.—The resting electrocardiogram (R) from a patient with cardiac infarction showing low T waves in leads II and CR7 and S–T depression in leads III and IIIR. These changes became exaggerated on exercise (E) and the S–T was particularly depressed in leads I, II and CR7.

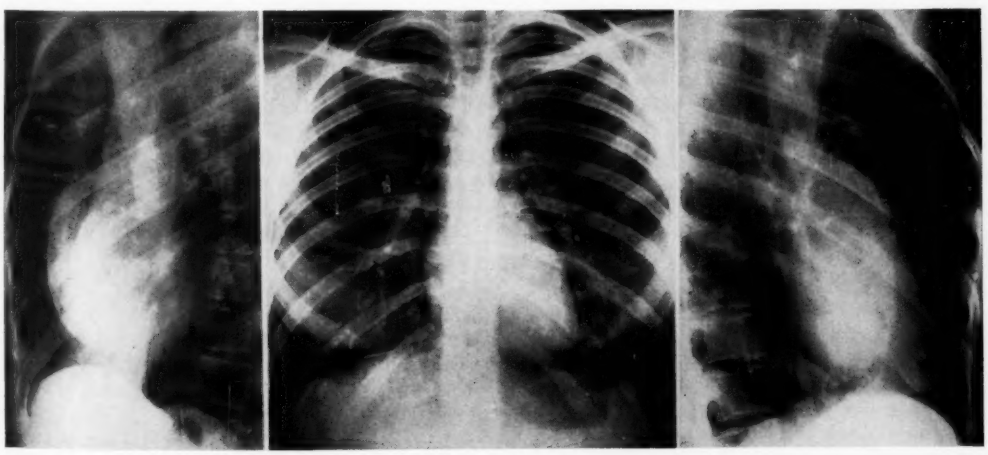

FIG. 3.—Teleradiogram (left oblique, anterior, and right oblique views) from a healthy subject showing the suspended heart. The inferior vena cava, in the oblique views, is exposed in its course from the diaphragm below to the elevated heart above.

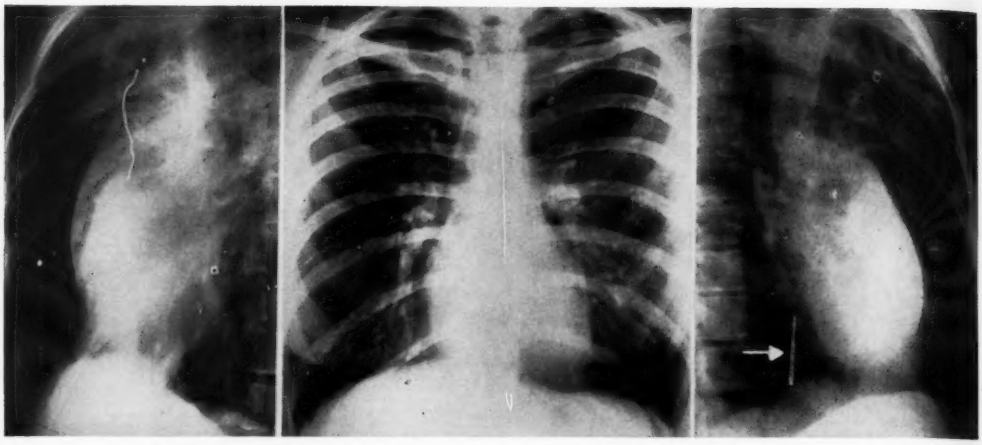

FIG. 4.—Teleradiogram (left oblique anterior, and right oblique, views) from a healthy subject showing the suspended heart. The inferior vena cava, in the oblique views, is exposed in its course from the diaphragm below to the elevated heart above; the arrow points to the line that indicates the vein's right border.

of the inferior vena cava obviously displayed (Fig. 3 and 4). There was no evidence of emphysema in any of the cases.

In a few patients in whom casual radiological examination suggested the characteristic appearance we have just described, the electrocardiogram was a normal tracing; a more critical radiological survey in such patients showed that although the heart appeared unusually elevated in relation to the diaphragm, a great part of the heart remained in contact with the diaphragmatic surface even during very deep inbreathing.

DISCUSSION

Changes in the electrocardiogram that take place as the result of an alteration in the position of the heart within the chest, and the manner in which its electrical potential is consequently readjusted, have often been described. Herrmann and Wilson (1922) concluded that the form of the natural electrocardiogram was not determined by the relative weight of the two ventricles, but depended chiefly upon the position of the heart and upon the arrangement of the ventricular conducting system; sometimes the one and sometimes the other of these factors exerted the greater influence. Katz and Robinow (1936) thought that the electrical field of the body was modified in accordance with the particular region of the heart that was in contact with the anterior chest wall, with the diaphragm, and with the posterior paravertebral muscle mass, which acted as good electrical conductors compared with the lungs which were poor conductors. Sigler (1938), writing on the changes in the cardiogram that took place in 100 cases when they assumed the standing and sitting posture from the recumbent, reported that in some instances the change was so gross as to cause the tracing to lose its identity from the one recorded in the other posture. Such changes did not conform to the theory based on Einthoven's triangle, for the shift in the electrical axis was not always the same as that predicted from the shift of the anatomical axis. Sigler concluded that the phenomenon was best explained by the change in contact of the adjacent conducting media with different portions of the heart resulting from alteration of body posture and that this produced a variation in conduction. Scherf and Weissberg (1941) from their observations on the effect of posture on the T wave in lead III, also concluded that these cardiographic changes followed an alteration in the contact taking place between the heart and the neighbouring tissues.

Writing on the electrocardiogram in its relation to the radiological configuration of the heart, Master (1942) described the long narrow heart in subjects with an asthenic habitus and with symptoms associated with neurocirculatory asthenia, and mentioned that in the past the terms hypoplastic, asthenic, drop, and emphysema heart, had been applied to it. In such cases where the diaphragm was depressed and the heart appeared elongated and vertical, the cardiogram was characterized by a low amplitude of the P and R waves in lead I and a high amplitude in leads II and III. Katz (1946) described the same tracing and stated that there was no unusual deviation in the S–T segment. A code of normality for the behaviour of the curve in lead III when repeated during deep inspiration (lead IIIR) was drawn up by Evans (1951). Thus, the P, R and T waves are expected to move upwards significantly, and without depression of the S–T segment, on deep inspiration. This is true for the large majority of healthy subjects, but in order that it might apply unexceptionally, it is necessary at cardioscopy to witness during the inspiratory phase a descent of the heart in unison with the diaphragm. Whenever this natural cardiodiaphragmatic relationship is maintained, depression of the T wave and of the S–T segment in IIIR confirms the existence of heart disease, provided also that it is not a digitalis effect.

Another distinctive electrocardiogram was described by Ylvisaker and Kirkland (1940) in a group of healthy young subjects in whom changes in the T wave in leads II and III, that could not be regarded as those accepted as variations of the normal, disappeared when the reclining position was assumed. In some of the cases a change into the upright position caused the T wave in lead II to become diphasic or iso-electric and in lead III to become inverted; a return to the recumbent position invariably reinstated the T wave in lead II to a normal configuration and amplitude, but a change in lead III was less constant and not so marked. Holzmann (1952) described the same cardiogram in subjects of subnormal body weight and with an asthenic habitus, where the P and R waves are tall in leads II and III and where the S–T segment and T wave are depressed predominantly in leads II and III and in chest leads over the left heart. He stated that such a tracing was obtained with the subject standing upright or fixed to a steeply inclined plane, and that the changes disappeared immediately on a return to the horizontal position. Goldberger (1953) proposed a remarkable explanation for such postural changes in the T wave; he postulated that in the upright position, when blood is pooled in the lower extremities, sympathetic stimulation following the transient drop in blood pressure causes a decrease in blood potassium and in turn reduces the amplitude of the T wave and depresses the S–T segment. If this were the explanation it is difficult to understand why the same changes should not be visible in the T wave in some of the other leads.

In this paper we describe an electrocardiogram that exhibits its special characteristics in the *reclining* position so that any postural manœuvre does not change its design, and for that reason cannot help its identification from the pathological variety met with in cardiac infarction. A somewhat similar tracing has been published by Master (1942) for his Fig. 24, taken from a youth aged 21 in whom radiological examination had shown a long and narrow heart, shows a cardiogram where the T wave was inverted in leads II and III. Master considered that clockwise rotation of the heart rather than impairment of the heart muscle had caused these changes. The fact that postural manœuvre fails to change this cardiogram into one of normal pattern, thereby establishing its innocent nature, creates a difficulty in telling it from the tracing that confirms the presence of cardiac infarction. In the pathological cardiogram, however, recorded in a patient the subject of cardiac pain, the existing S–T depression is exaggerated following strenuous physical exercise. In the innocent cardiogram, although the changes at rest were similar to those in the pathological tracing, they were not exaggerated by exercise; and at the same time specific radiological appearances connected with the peculiar position of the heart were found to be present.

We examined the electrocardiogram in 33 patients with pulmonary emphysema in whom radiology of the chest had shown a low and rather immobile diaphragm and a centrally placed heart that looked small and slender in all but three cases where it was enlarged. In 27 of these the electrocardiogram was physiological; in the three with cardiac enlargement the tracing showed

right heart preponderance; in the remaining three the electrocardiogram was similar to the one we describe in this paper, but the S–T segment was not depressed in CR7.

The separation of the suspended heart from its close contiguity with its surrounding structures, particularly the diaphragm, disturbs the anatomical medium that customarily transmits the varying electrical potential generated by cardiac contraction, and this we consider gives rise to changes associated with this characteristic cardiogram.

Summary and Conclusions

In the absence of digitalis therapy, depression of the S–T segment in the electrocardiogram recorded in the reclining position is usually accepted as evidence of myocardial injury from coronary arterial disease or as a sign of ventricular hypertrophy. In a group of patients, however, we found it inappropriate on clinical grounds to apply so sinister a meaning to this cardiographic sign, and for this reason we assembled 13 such cases for special investigation.

Each tracing showed depression of the S–T segment in leads III and IIIR (lead III recorded during deep inspiration), and lesser depression in leads II and CR7, and it remained materially unaltered by a change to the upright posture. The cardiogram resembled that found in cardiac infarction involving the lateral and postero-inferior portion of the left ventricle. The innocent tracing that we describe here, differed however, from the pathological kind in two ways, namely that strenuous physical exercise failed to increase the deformity and that it was associated with characteristic radiological changes.

Chest pain had brought the heart under suspicion in 9 of the 13 patients, although almost invariably, either in regard to its character, distribution, or its response to exercise and rest, it failed to conform to the tenets customarily applied to true cardiac pain. Although two patients were over 65 the fact that eight were under 30 years of age was foremost in suggesting that cardiac infarction had not caused the cardiographic irregularity which it so closely resembled.

Radiological examination of the heart disclosed an appearance that proved to be common to all cases and indicated a peculiar stance of the heart as the explanation for the abnormal electrocardiogram. In the *anterior* view casual examination often discovered nothing more than a naturally placed heart, but during deep inspiration the left cardiophrenic junction moved noticeably towards the middle and the angle narrowed correspondingly; on the right side the cleavage between the right atrium and the diaphragm laid bare the inferior vena cava as it traversed this gulf. During inspiration in the *right oblique*, the heart aloft and the diaphragm below separated widely, and again brought the inferior vena cava, which coursed slantwise across the gap, into great prominence. Similarly in the *left oblique* view the heart during inspiration was lifted some way above the depressed diaphragmatic platform to which it appeared anchored centrally by the inferior vena cava.

The recognition of these characteristic electrocardiographic and cardioscopic findings, featuring the syndrome of the *suspended heart*, should avoid the erroneous diagnosis of coronary arterial disease in subjects in whom chest pain is associated with a depression of the S–T segment in the electrocardiogram.

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EPILEPSY AND MITRAL STENOSIS

BY

C. G. BAKER AND T. R. L. FINNEGAN

From the Cardiac Department, Guy's Hospital

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It has been recognized for a long time that epileptic convulsions may occur at the onset of or following cerebral infarction (Gowers, 1885; Hughlings Jackson, 1876; and Savill, 1909). It has been pointed out also that the incidence of epilepsy is higher in those suffering from rheumatic heart disease than in the general population. Chadbourne in 1903 while working in the Ohio Hospital for Epileptics noted that 5 per cent of the patients had rheumatic heart disease, and more recently Foster (1942) and Bruetch (1942) have made similar observations.

The ætiology of the epileptic seizures with rheumatic heart disease is not so clearly understood. Most writers state that seizures may occur in those with cardiac arrhythmia when momentary failure of cardiac output leads to cerebral anoxia (Symonds *et al.*, 1950). Others have claimed that the epilepsy is secondary to rheumatic obliterative arteritis affecting the cerebral vessels, and Bruetch (1942) describes three cases in which epilepsy occurred in patients who had rheumatic heart disease and evidence of multiple cerebral infarctions at autopsy, with histological changes that he interpreted as due to rheumatic arteritis. It has not been appreciated how frequently epilepsy in association with rheumatic heart disease could be due to emboli from the left atrium. Such emboli may cause infarction in vital areas of the brain, sometimes ushered in by a seizure and subsequently giving rise to epileptic attacks, associated with evidence of permanent cerebral damage; some, however, could cause infarction in "silent" areas of the brain and give rise to no immediate symptoms other than perhaps a momentary faint feeling, but could later develop into foci of epileptic activity.

A series of cases is presented in which emboli were thought to be the cause of the epileptic seizures. Since 1950, when a preliminary report of the success of operative treatment for mitral stenosis was made (Baker *et al.*, 1950) a large number of patients with this disease has been seen at Guy's Hospital. The occurrence of epilepsy with mitral stenosis was noted in some of the earlier patients and it was thought that this was a causal rather than a chance association of two common conditions. Since then, 22 patients have been seen where these two conditions were present and it is this group we are here reporting. Although some patients may have been missed, particularly in the large number who came in the earlier years when mitral valvotomy was not widely practised, we have not excluded any patient where epilepsy and mitral valve disease were both present. It is estimated that these 22 patients were collected from a total of about 600 who were seen with mitral valve disease. This large number was in itself a selected group as regards severity, for the great majority was referred with operative treatment in view.

Analysis of the Cases

The essential details are set out in the Table. There were 15 women and 7 men and the ages when first seen ranged from 19 to 47 with an average of 34 years. The sex and age incidence are in keeping with the large group of patients with mitral disease from which they were selected. Although it must be admitted that the family history was not studied in great detail there is only one patient (Case 20) with a family history of epilepsy. The age of onset of fits ranged from 19 to 47,

TABLE

PATIENTS WITH EPILEPSY AND MITRAL STENOSIS

No. and sex	Age at onset of fits	Age at onset of cardiac disability	Rhythm at onset of fits	Systemic embolism	Degree of mitral valve disease	Operative findings			Type of epy.	E.E.G.
						Size in cm.	Ca.	Age		
1F	47	47	Sinus	Hemiplegia	Severe MS	1×0·5	—	48	Focal	Focal
2F	19*	17	Sinus	—	Severe MS and MI	1×0·3	Yes	19	Major	Abnormal
3M	41	39	Sinus	—	Severe MS (MI)	1·0	Yes	42	Major	Normal
4F	36	20	A.F.	—	Severe MS (TI)	0·8×0·4	—	43	Major	Abnormal
5F	34	23	Sinus	—	Severe MS	Refused valvotomy			Major and minor	Focal
6F	39	24	A.F.	1 Cerebral 1 Leg	Severe MS	0·5×0·3‡	—	39	Minor and focal	Abnormal
7F	41	27	A.F.	1 Mesenteric 1 Arm	Severe MS	0·75×0·25	Yes	42	Major	Abnormal
8M	34	26	A.F.	Hemiplegia	Severe MS and MI	Op. not advised Died aged 39			Minor focal	Normal
9F	29	None at 43	Sinus	—	Mild MS	Op. not advised			Major	Abnormal
10M	33*	24	A.F.	—	Severe MS (TI)	1·4×2·0	Yes	32	Minor focal	—
11M	32	27	A.F.	1 Cerebral	Severe MS	1·2×0·8	Yes	32	Minor focal	Focal
12F	20	29	Sinus	—	Moderate MS (AI)	Op. not advised			Major	Abnormal
13F	33	26	Sinus †	—	Severe MS (AI)	1·5×1·0	Yes	36	Major	Normal
14M	33	20	A.F.	Hemiplegia 2 Renal	Severe MS (AI)	0·3×0·7	—	30	Major and minor focal	—
15F	33	24	A.F.	Hemiplegia	Severe MS	0·5×0·4‡	—	34	Minor focal	Abnormal
16F	18	22	Sinus	—	Moderate MS (AI)	Op. not advised			Major focal	Focal
17M	28	28	A.F.	Hemiplegia	Severe MS	"Small"	Yes	32	Minor focal	Normal
18F	30*	23	Sinus	—	Severe MS	1·0	—	29	Minor focal	Abnormal

Table—*continued*

No. and sex	Age at onset of fits	Age at onset of cardiac disability	Rhythm at onset of fits	Systemic embolism	Degree of mitral valve disease	Operative findings			Type of epy.	E.E.G.
						Size in cm.	Ca.	Age		
19F	25	25	A.F.	Hemiplegia 1 Leg	Severe MS (MI)	1·5‡	Yes	27 —	Major	Borderline
20F	28	28	A.F.	—	Severe MS	0·75‡	—	30	Major and focal	Focal
21F	36	36	A.F.	Hemiplegia	Moderate MS (AS)	Op. not advised			Major and focal	Focal
22M	34	35	Sinus	—	Severe MS	0·5	Yes	45	Major and minor	—

No patient had a family history of epilepsy except Case 20.
* In these three, the fits started after mitral valvotomy, after 4 months in Case 2, after 5 months in Case 10, and after 6 months in Case 18.
† This patient had paroxysms of auricular fibrillation.
‡ There was an old thrombus in the left atrium at operation in these four patients.

with an average of 32 years, which is a late onset for idiopathic epilepsy. In all but 4 patients the onset of fits occurred after the onset of symptoms from mitral disease. In two of these (Cases 9 and 12) where epilepsy preceded disability from mitral disease, which in neither case was severe, the clinical evidence pointed to a diagnosis of idiopathic and post-concussional epilepsy respectively. In the remaining 18 patients the fits occurred when the heart disease was already advanced and in only two (Cases 16 and 21) was the disability other than severe. The absence of a family history of epilepsy except in one, the late onset, and the fact that they followed disability from mitral disease, all suggest that the fits are a direct consequence of that condition. When we first noted this association we considered that the epilepsy was due to or followed a cerebral embolism, and an analysis of the 20 patients, excluding Cases 9 and 12 where idiopathic and post-traumatic epilepsy were diagnosed, supports this explanation.

Embolism from mitral disease is most likely to occur in three circumstances: with the onset of atrial fibrillation which favours the formation of clot in the left atrium and atrial appendage; secondly, with mitral valvotomy where clots may be detached at operation or soon after; and thirdly, with tight mitral stenosis and high atrial pressures—particularly if there is extreme rigidity or calcification of the valve—where clots may form and be detached even when the rhythm is regular, and when there is no operative interference. These three points can be considered with reference to the data in the Table.

Twelve of the twenty patients were fibrillating when fits started; in six of these the fits followed within a few months of the onset of fibrillation and in a further four they followed within a year of a hemiplegia due to a cerebral embolism, occurring shortly after fibrillation. Of the eight in sinus rhythm, one (Case 13) had paroxysmal attacks that were probably atrial fibrillation for the arrhythmia was established three years later. Systemic embolism is not uncommon in mitral stenosis with sinus rhythm; in a series of 150 patients followed up at Guy's after mitral valvotomy there were 31 with a history of previous embolism and 8 of these were in sinus rhythm at the time.

Three patients developed fits after mitral valvotomy. One of these (Case 10) developed fibrillation as the result of operation, the other two (Cases 2 and 18) were in sinus rhythm when fits started, though both developed fibrillation later in the fourth year after mitral valvotomy.

Eighteen of the twenty patients had severe mitral disease and sixteen of these were treated surgically; one refused operation and one with significant mitral incompetence as well as stenosis was not advised to have an operation and died with heart failure. The other two patients both had moderate disability, were not deteriorating, and surgical treatment is being held in reserve. It is interesting that neither of the two patients where epilepsy was not thought to be secondary to embolism had severe mitral valve disease. The state of the mitral valve in the sixteen patients treated by valvotomy is shown in the Table. All but four had mitral stenosis without regurgitation. One (Case 2) had significant mitral incompetence found at operation, two (Cases 3 and 22) had an insignificant regurgitant jet through a calcified valve, and the fourth who was thought to have mitral incompetence (Case 8) was not advised to have an operation and subsequently died. Nine of the sixteen patients had calcified valves, which is a higher proportion than was found in the series followed up at Guy's (29 out of 150). In only one (Case 10) was the valve not tightly stenosed and this patient developed Jacksonian epilepsy after valvotomy.

A clot was found in the left atrium at operation in only four of the sixteen patients who had mitral valvotomy, although three had had previous cerebral embolism. This is in keeping with the experience in the Guy's series of 150 patients already referred to, where clot was found at operation in only 13 who gave a history of previous systemic embolism, while clot was found in 17 where there was no history of embolism. It is in fact the clot that does not remain attached in the left atrium that causes systemic embolism.

On the basis of the three factors of atrial fibrillation, mitral valvotomy, and severe distortion of the mitral valve, it will be seen that the circumstantial evidence suggesting that cerebral embolism is the cause of the epilepsy is strong.

There is further evidence pointing to this explanation. Nine of the twenty patients had clear clinical evidence of a cerebral embolism and seven of them had a hemiplegia, though only two (Cases 1 and 15) were left with any permanent disability after this. Four of these patients had clinical evidence of systemic embolism other than cerebral. The fits in thirteen of the twenty patients had focal features and in six of these the electroencephalogram showed evidence of a focal lesion. The electroencephalogram was normal in four patients (Cases 3, 8, 13, and 17), and was not done in Case 10; two of these had focal and two major epileptic attacks.

Reviewing all the evidence in these twenty-two patients there are two (Cases 9 and 12) where we think that the epilepsy is respectively idiopathic and post-concussional in origin. In the remaining twenty there are three where the epilepsy could be independent of the mitral valve disease, Case 4 where there is a history of meningitis in childhood and Cases 13 and 22 where it might be idiopathic. We think, however, that in these three patients the epilepsy was due to cerebral embolism and would add them to the remaining seventeen where the evidence is convincing.

Practical Considerations

The recognition that fits may occur as the result of cerebral embolism, whether clinically obvious or not, has practical advantages. Several of our patients were suspected of having multiple attacks of embolism when in fact the repeated attacks were epileptic and due to a previous cerebral embolism. Repeated systemic embolism would be a reason for advising valvotomy and although in most cases this may be necessary on account of the cardiac state alone, it may not be so, as in our Cases 16 and 21.

Of more practical importance to the patients was the fact that the fits had all been considered to be "heart attacks" due directly to their mitral disease and not one of them had been given sedative treatment to control their epilepsy. When this diagnosis was made and the appropriate treatment was given, there were no further fits except in four patients (Cases 1, 3, 6, and 15), and in two of these four a fit occurred only in the post-operative period when the sedative treatment had been temporarily discontinued. The practical advantage of making the diagnosis of epilepsy due to a previous cerebral embolism is well illustrated in Case 21.

Case 21. The patient, a woman of 46, was referred for an opinion as to the necessity for mitral valvotomy. She had been fibrillating for 15 years and 10 years before had had a left-sided hemiparesis from which she recovered fully. Since then she had had at least twenty attacks of sudden loss of consciousness, which had been diagnosed as repeated cerebral emboli. The doctor wrote "The only people who are not frightened by these occurrences now are the patient, who is unconscious, and myself who have seen so many of them". In the month before coming to hospital two attacks had been associated with abdominal pain before consciousness was lost, and the possibility of mesenteric embolism had been raised. When she attended as an out-patient, she was found to be mentally clouded, although her last attack had been seven days before, and as it was thought inadvisable for her to make the train journey home she was admitted as an emergency under the care of Dr. W. N. Mann, who diagnosed epilepsy following a previous cerebral embolism. It was several days before she made a complete recovery of mental function and for the first few days there was weakness and inco-ordination of the left side. In addition to her mitral stenosis there were signs of aortic stenosis, but as her cardiac reserve was adequate and there was no evidence of cardiac deterioration operation was not advised. On epanutin and phenobarbitone she had had no further attacks when seen four months later.

Summary

The association between epilepsy and rheumatic heart disease is noted and the possible ætiology of the epilepsy is briefly discussed.

Twenty-two cases are reported where epilepsy occurred in association with mitral stenosis. The cases are analysed and it is concluded that in twenty of them the epilepsy was due to previous cerebral emboli.

The importance of recognizing the true nature of these attacks is emphasized and the response to anticonvulsant drugs was found to be very satisfactory.

We wish to acknowledge the help given by Dr. G. Pampiglione who reported on and analysed the electroencephalograms, and Dr. W. N. Mann for providing Case 21.

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OBSCURE CARDIOPATHY

BY

BYRON EVANS

From the United Cardiff Hospitals

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When true cardiac enlargement is found in a patient without evidence of hypertension, coronary arterial disease, valvular defects, congenital lesions, bronchopulmonary disease, or thyrotoxicosis, the ætiology becomes obscure. Such patients often present with arrhythmia or with symptoms and signs of heart failure, and cardiac enlargement is found clinically and by cardioscopy: the heart failure eventually becomes resistant to treatment. After necropsy and microscopical examination of the heart, the actual cause of the illness may still remain obscure. This problem is not uncommon and the object of this paper is to describe four such cases.

The main clinical features are shown in Table I and the necropsy findings in Table II.

TABLE I

MAIN CLINICAL FEATURES

Case	Sex	Age	Family history	Signs	Blood pressure	Electrocardiographic changes	Cardioscopy	Interval between onset of symptoms and death, and mode of death
1	M	28	Nil	Triple rhythm. Transient S.M. at apex	120/80	A.F. Wide QRS. Deep Q in 1, V4, V6. Inverted T in V6	R.V. ++ L.V.++	2 yr. Heart failure. (Previous pulmonary infarcts)
2	M	47	Nil	No murmurs	120/70	E. S. Partial L.B.B.Bl.	R.V.++ L.V.++	5 yr. Sudden. (Previous heart failure)
3	M	51	Nil	S.M. at apex	130/80	P–R interval long. R.B.B.Bl. Later A.F.	RV.++ L.V.++	3 yr. Heart failure. (Previous splenic and renal infarcts)
4	F	41	Nil	Triple rhythm. S.M. at apex	120/80	A.F. Inverted T in V6	R.V.+ L.V.+	2 yr. Heart failure. (Previous splenic and renal infarcts)

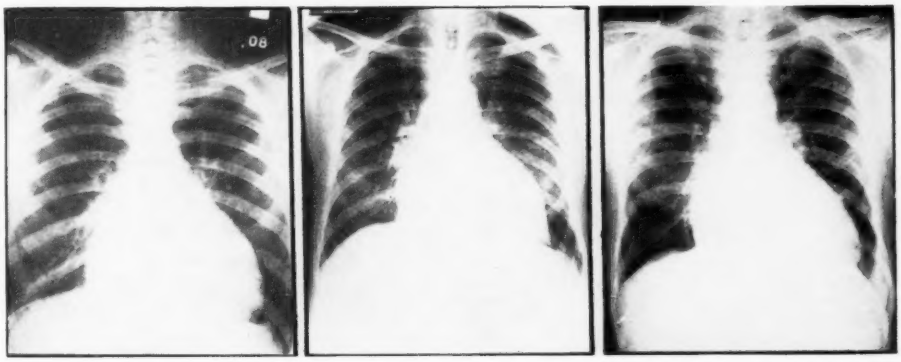
CASE REPORTS

Case 1. A man, aged 28, had served in the Merchant Navy visiting many countries, including East and West Africa. His parents and four sisters and one brother had healthy hearts. Five months previous to his admission to hospital mass miniature radiography had shown moderate cardiac enlargement. His main symptoms were cough, breathlessness, hæmoptysis, and swelling of the legs. There were gross signs of heart failure. Auricular fibrillation was present and the heart was much enlarged and this was confirmed radiologically (Fig. 1A). The heart sounds were normal, no murmurs were heard, and the blood pressure was 120/80 mm. Hg. Pericardial effusion was suspected at one stage, but fluid was not obtained by aspiration. The cardiogram (Fig. 2) showed auricular fibrillation, low voltage, wide QRS complexes, deep Q

TABLE II

SUMMARY OF NECROPSY FINDINGS

Case	Weight (grams)	Thickness of R.V. (mm.)	Thickness of L.V. (mm.)	Ante-mortem thrombus	Coronary arteries	Histological changes
1	740	10	20	Present	Small right and circumflex of left. All patent	Interstitial and endocardial fibrosis. Hypertrophy of muscle fibres
2	620	6	19	Absent	Small right. All patent	Slight sub-endocardial and focal myocardial fibrosis. Marked hypertrophy of muscle fibres
3	560	7	10	Present	Normal size and patent except for lumen of left descending branch which was one-third occluded	Diffuse myocardial fibrosis
4	405	5	14	Present	Normal size and patent. Localized eccentric intimal thickening of left	Focal and diffuse myocarditis. Endocardial and myocardial fibrosis



A B C

FIG. 1.—(A) Symmetrical enlargement of the heart. Case 1. (B) Great enlargement of the heart with early pulmonary congestion. Case 2. (C) Cardiac enlargement predominantly to the left with a small left-sided effusion. Case 3.

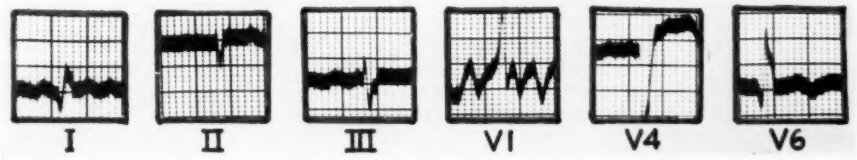


FIG .2.—Auricular fibrillation; wide QRS complexes; deep Q waves in 1, V4, and V6; and inverted T waves in V6. Case 1.

waves in leads 1, V4, and V6, and inverted T waves in V6. The blood count, plasma proteins, and blood urea were within normal limits, and the Wassermann and Kahn reactions were negative. He remained in hospital for six months and eventually the signs of heart failure disappeared, but he was subsequently readmitted three times because of heart failure. He developed a triple rhythm and a transient musical systolic murmur was occasionally heard in the mitral area. He died after repeated pulmonary infarctions and the terminal development of gangrene of his toes and heels.

At necropsy by Dr. T. E. Parry, the pericardium was found to be normal and the cavity contained about 110 ml. of clear straw-coloured fluid. The heart was grossly enlarged and weighed 740 g. The right atrium was dilated and its walls thickened. Both ventricles were dilated and hypertrophied (R.V. 10 mm., L.V. 20 mm. thick). The valves were normal. Several adherent antemortem mural thrombi were present in both atria. One of these protruded from the left atrium through the dilated mitral valve producing a ball-valve obstruction of the orifice (Fig. 3). The endocardium of the atria was slightly thickened and that of the ventricles was thin and translucent. White streaks and patches of fibrosis were evident

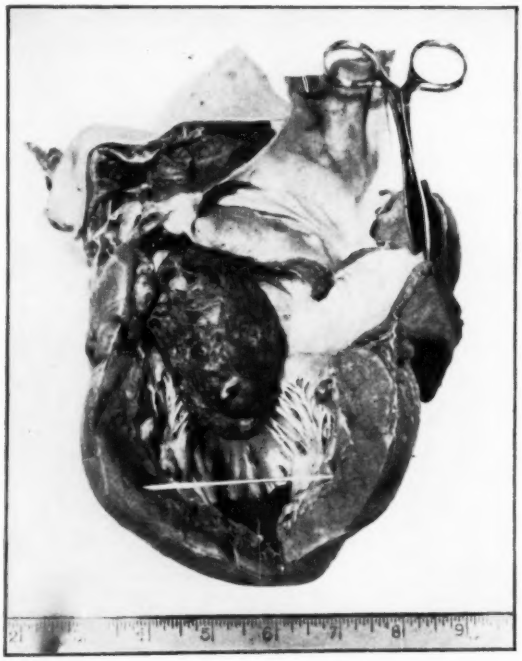


FIG. 3.—Hypertrophy of left ventricle; a large mural thrombus protruding through the mitral valve. Case 1.

on the cut surface of the wall of the left ventricle. The aorta was smaller than normal. The two coronary arteries arose normally from the aorta and were free of atheroma. The right coronary artery, and in particular, the circumflex branch of the left coronary artery were small having regard to the size of the ventricles. The left pleura contained a hæmorrhagic effusion and several infarcts were present in the lungs. Microscopical examination of the atria showed hypertrophy of the muscle fibres and a moderate degree of interstitial and endocardial fibrosis, and the ventricular walls showed a pronounced degree of interstitial fibrosis with hypertrophy of the muscle fibres (Fig. 4). Aschoff nodes were not seen.

Case 2. A man, aged 47, had served in the Army from 1941 to 1946 and had been in Burma and West Africa. His father was alive and well and had extrasystoles. His mother died of rheumatic valvular disease which was proved at necropsy. Five years before he died he began to have paroxysms of tachycardia and his heart then was of normal size. These attacks recurred at intervals, and for two

months before he was seen the tachycardia had persisted. During this time he had become breathless with swelling of his legs. On admission to hospital he was cyanosed and orthopnœic, the pulse was rapid and irregular from extrasystoles, and the apex beat was displaced to the anterior axillary line. The sounds were normal, no murmurs were present, and the blood pressure was 120/70 mm. Signs of heart failure were present. On cardioscopy (Fig. 1B) there was great enlargement of the heart with pulmonary congestion. Serial radiographs during the next five months showed no appreciable change in the appearances. The electrocardiogram (Fig. 5) showed extrasystoles, wide QRS complexes, and partial left bundle-branch block. Further cardiograms were taken at weekly intervals and these showed wider QRS complexes

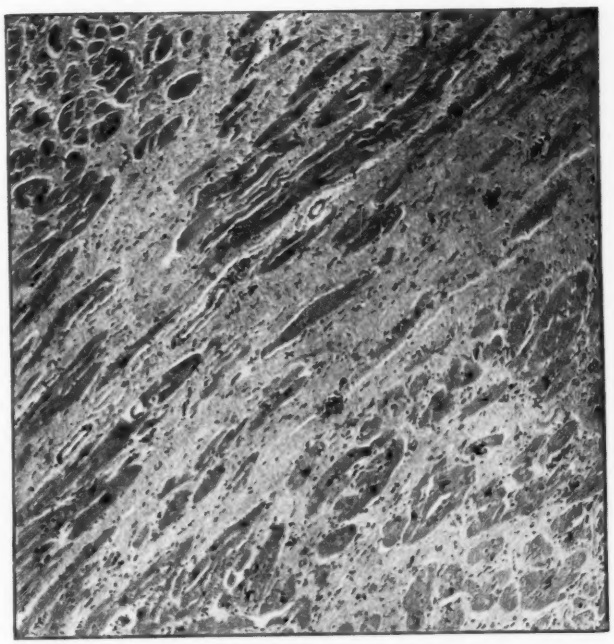


FIG. 4.—Interstitial fibrosis and hypertrophy of muscle fibres of myocardium of right ventricle. ×58. Case 1.

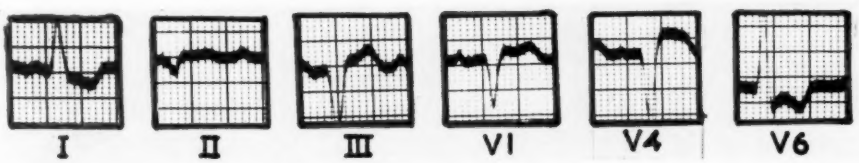


FIG. 5.—Extrasystoles; wide QRS complexes; and partial left bundle-branch block. Case 2.

and coupling. The blood count and plasma proteins were normal, and the Wassermann and Kahn reactions were negative. He responded to treatment and the signs of failure disappeared. Digitalis therapy was continued on leaving hospital and he resumed his occupation as a clerk. Two years later he died suddenly in the street.

At necropsy by Dr. W. R. L. James, the pericardium was found to be normal. The heart was enlarged and weighed 620 g. The enlargement affected both sides of the heart equally. The wall of the right

ventricle measured 6 mm. and that of the left 19 mm. in thickness. The right coronary artery had a small ostium and was small throughout its length without atheroma, the left showed a slight degree of atheroma near its origin, and both were patent. The heart muscle was thick but otherwise normal to the naked eye. There was no defect of the valves, endocardium, or of the septa of the heart. The aorta was normal. Microscopical examination showed that the heart muscle fibres were enlarged and there was slight vacuolation of the cytoplasm in the region of the nuclei, and slight fibrosis of the subendocardial zone of the myocardium. Throughout the heart muscle there were scanty foci of fibrosis, the largest being less than 2 mm. across. There was a very slight increase of the perivascular connective tissue (Fig. 6). Special staining of the myocardium did not show any accumulation of lipoid material.

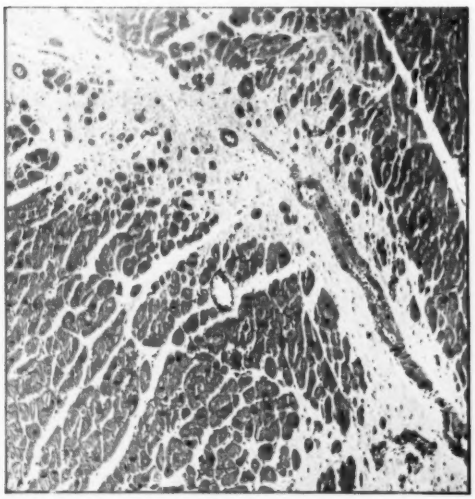


FIG. 6.—Slight increase in fibrous tissue and hypertrophy of muscle fibres of myocardium of left ventricle. ×46. Case 2.

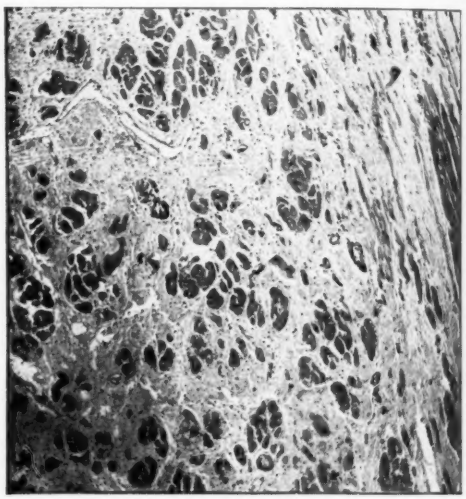


FIG. 7.—Myocardium of left ventricle, showing diffuse fibrosis. ×46. Case 3.

Case 3. A man, aged 51, was employed as a clerk and had never been abroad. His father had died at the age of 28 and the cause of death was unknown. His mother, aged 78, was alive and well. Two years previously he had been breathless. A systolic murmur heard in the mitral area was thought to be due to mitral valve disease and on cardioscopy there was enlargement of the left ventricle, but no good evidence of left atrial enlargement. On the day previous to his admission to hospital he had experienced difficulty in speaking, but within two minutes he recovered. He also had some weakness of his right limbs, but was able to walk to the hospital where he showed signs of a right hemiparesis. The pulse rate was 68 and irregular from extrasystoles. The apex beat was displaced to the anterior axillary line. There was a harsh systolic murmur in the mitral area. The blood pressure was 130/80 mm. and there were no signs of heart failure. The weakness of the right limbs slowly improved, but three weeks after admission he showed signs of heart failure that persisted in spite of treatment. The blood count, serum proteins, and serum electrolytes were normal. On cardioscopy (Fig. 1C) there was cardiac enlargement mainly of the left ventricle, but slightly of the right ventricle. The cardiogram (Fig. 8) showed low voltage, prolonged P–R interval, wide QRS complexes, and right bundle-branch block. Later he developed auricular fibrillation. He died with signs of cardiac failure three years from the start of his illness.

At necropsy by Dr. R. A. Parker, the pericardium was found to contain 20 ml. of clear straw-coloured fluid. There was slight fibrinous pericarditis over one area 3 cm. across. The heart was enlarged and weighed 560 g. The left ventricle was dilated and its wall measured 10 mm. in thickness; the right was hypertrophied and its wall measured 7 mm. in thickness. There was a mural thrombus 3 cm. across at the apex of the left ventricle. The valves and septa were normal. The coronary arteries were normal and without atheroma with the exception of 1 cm. in the left descending branch where the lumen was one-third

FIG. 8.—Prolonged P–R interval; wide QRS complexes; and right bundle-branch block. Case 3.

occluded. There was an old area of softening 1 cm. across in the internal capsule of the brain. Chronic venous congestion of the liver, left pleural effusion, and infarcts in the spleen and the right kidney were also found. Microscopical examination showed diffuse fibrosis of the myocardium (Fig. 7). The myocardium under the thrombus showed the same changes.

Case 4. A Jamaican woman, aged 41. Her father died at the age of 57 as a result of an accident and her mother at the age of 80 from an unknown cause. There was no family history of heart disease and each of her six children had a normal-sized heart. Five years before her admission to hospital she had developed a cough and a radiograph at that time showed slight cardiac enlargement. Five weeks before she was seen she became breathless on exertion and this became progressively worse, and was followed by swelling of the legs. There were gross signs of heart failure. The pulse rate was 130 and the rhythm regular. The apex beat was displaced one inch beyond the mid-clavicular line. There was a triple rhythm present and a soft systolic murmur in the mitral area. The blood pressure was 120/80 mm. On cardioscopy there was generalized cardiac enlargement affecting both ventricles. The cardiogram showed sinus tachycardia and inverted T wave in V4. She responded well to treatment and was discharged two months later. Within four months she developed auricular fibrillation which was controlled by digitalis therapy. She continued to be breathless on slight exertion and fifteen months later was readmitted in gross cardiac failure which again responded to treatment. During this admission she showed signs of renal and splenic infarction. On cardioscopy, the heart was larger and the electrocardiogram (Fig. 9) confirmed the auricular fibrillation

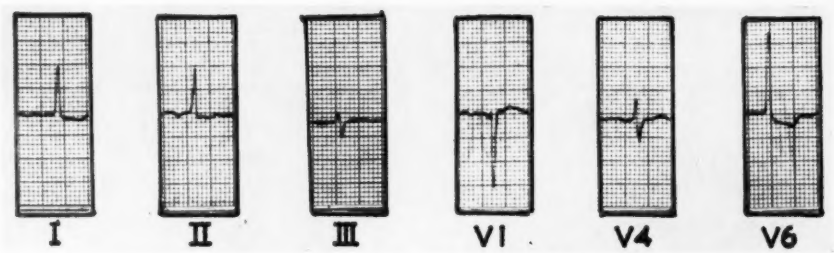


FIG. 9.—Auricular fibrillation; and inverted T waves in V6. Case 4.

and showed inverted T waves in V6. The blood count was normal. Dr. I. A. B. Cathie tested the patient's serum for toxoplasmosis and found that the dye test was positive at 1/16 and that the complement fixation test was negative. The Wassermann and Kahn reactions were negative. She was discharged from hospital but one month later was readmitted in a moribund condition with signs of pulmonary œdema and died the same day.

At necropsy by Dr. F. K. Storring, the pericardium was found to contain 160 ml. of straw-coloured clear fluid. The heart weighed 405 g. There was dilatation and hypertrophy of the left ventricle, 14 mm. thick, dilatation of the right ventricle, 5 mm. thick, right atrium, and right auricle. All the valves were normal and the chordæ tendineæ were thin. The endocardial lining of the chambers of the right side of the heart appeared normal, but that lining the left side of the heart was thickened. The endocardial thickening was greater in the left atrium and auricular appendage than in the left ventricle. The coronary arteries were patent throughout; their walls were thin except for the left coronary artery which showed an eccentric thickening of its intima just distal to the point of origin of the anterior descending branch. The muscle did not show any macroscopic abnormality. Congested and œdematous lungs, chronic venous congestion of the liver, and infarcted areas in the spleen and kidneys were also found. Microscopical

examination of the heart showed interstitial perivascular and patchy focal fibrosis (Fig. 10) with diffuse infiltration of the interstitial connective tissue with chronic inflammatory cells composed mainly of lymphocytes, plasma cells, mononuclear cells with somewhat large basophilic cytoplasm, and degenerative cells with pyknotic nuclei. In addition, focal collections of similar chronic inflammatory cells were occasionally seen in the areas of perivascular fibrosis in relation to the vessels (Fig. 11) as well as in the patchy areas of fibrosis with evidence of muscle destruction in the latter. The endocardium of the left ventricle, including the interventricular septum, the left atrium, and left auricle was thickened. In the section taken from the left auricle a small organized mural thrombus was present. The left coronary artery showed at one point an eccentric atheromatous thickening but it was patent.

FIG. 10.—Myocardium of left ventricle, showing area of fibrosis. ×46. Case 4.

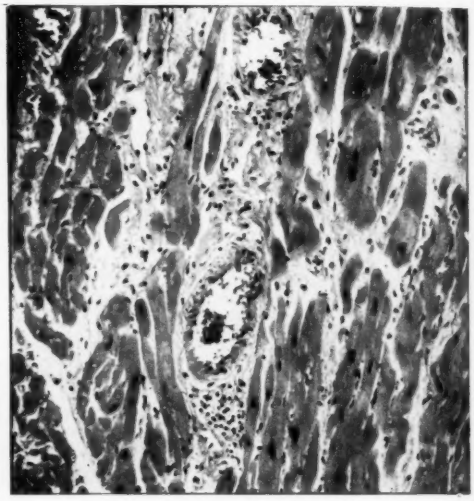


FIG. 11.—Myocardium of left ventricle, showing perivascular and interstitial fibrosis with lymphocytes and plasma cells in relation to coronary vessels. ×110. Case 4.

DIAGNOSIS

The conditions that suggested themselves before a diagnosis of myocardial fibrosis was made in these cases were pericardial effusion, constrictive pericarditis, coronary artery disease, mitral valve disease, and thyrotoxicosis. The radiological interpretation in the first case favoured a pericardial effusion and the diagnosis was so much in doubt at first that an exploring needle was introduced, but no fluid was obtained. The presence of a very large heart and the absence of greatly distended cervical veins and liver and of a sound in early diastole appeared to rule out the diagnosis of constrictive pericarditis. In the second case the paroxysms of tachycardia and the cardiographic tracings at one stage suggested coronary arterial disease, but later curves failed to substantiate this diagnosis. Mitral valve disease was thought to be present in the third case at first because of the loud systolic murmur in the mitral area, but cardioscopy failed to show an enlarged left atrium. When the fourth patient developed auricular fibrillation it was thought that thyrotoxicosis might have been missed, but she derived no benefit from antithyroid therapy. No attempt has been made to include all the diseases that enter into the differential diagnosis of cases that present with cardiomegaly, and mention has only been made of the conditions that were considered in these particular cases.

Discussion

Bedford and Konstam (1946) recorded a series of 40 cases with endomyocardial fibrosis occurring in African soldiers, all of whom had cardiomegaly and signs of heart failure: necropsy in 17 showed normal coronary arteries but some subendocardial necrosis and fibrosis, endocardial fibrosis, and hypoplasia of the aorta. They did not know the cause of this syndrome, but considered whether nutrition or a constitutional factor associated with the aortic hypoplasia might be operative. Similar lesions were found in 20 Africans reported by Ball *et al.* (1954): of these, 10 had mitral incompetence, 2 had tricuspid incompetence, and 2 had both these lesions; 4 had healthy valves and 2 had extensive endocardial fibrosis of the right ventricle with distortion of the cavity to such a degree as to almost obliterate the tricuspid orifice. The lesions were essentially fibrosis of the endocardium and underlying myocardium at or near the apex of the ventricles with thrombus formation on the abnormal endocardium, the fibrous tissue spreading upwards and involving the papillary muscles, chordæ, and cusps. Histologically, cellular fibrous tissue was found in the thickened endocardium and strands of this tissue penetrated into the myocardium. No cause was found for the condition but virus infection, some antigen-antibody reaction, and malnutrition were considered possible ætiological factors. In the cases reported here the essential fibrotic lesions were found in the myocardium and are therefore unlike those described by Konstam and Bedford and by Ball *et al.* The endocardium was only slightly involved in the disease process in the first two cases and in Case 4 the thickened endocardium was more prominent in the left atrium than in the left ventricle, and in this case the main lesions were those of chronic diffuse interstitial myocarditis. No signs of progressive liver disease were found in these cases and they were therefore dissimilar from the 30 Bantu patients described by Gillanders (1951). Becker *et al.* (1953) described 40 cases that died from heart failure: at necropsy the heart showed dilatation without hypertrophy, subendocardial necrosis or fibrosis, fibrosis of the papillary muscles, and focal or diffuse thickening of the endocardium. The microscopical picture was that of degeneration of collagen and its associated ground and cement substances. Widespread focal involvement of the connective tissue throughout the body was demonstrated. Most of their cases had a prolonged pyrexia and the average duration of life was six months. The clinical picture and the necropsy findings are quite unlike the four cases described here. Paulley *et al.* (1956) has recently recorded four cases of myocardial toxoplasmosis presenting as cardiomegaly with positive serological tests: the tests were only performed in Case 4 and they were negative.

The four cases recorded here had cardiac hypertrophy with no signs to indicate the more common causes of heart disease. All had abnormal electrocardiograms and even in the reported cases of myocardial fibrosis right bundle-branch block (as shown in Case 3) is rare. Three had embolic phenomena and all showed signs of heart failure. The microscopical findings, although similar, were not identical in all the cases—interstitial fibrosis, slight endocardial fibrosis, and hypertrophy of the muscle fibres in the first; very slight subendocardial and focal fibrosis with much muscle fibre hypertrophy in the second; diffuse fibrosis of the myocardium in the third; and active diffuse interstitial myocarditis with myocardial and endocardial fibrosis in the fourth case. They all showed, however, a fibrotic reaction in the myocardium.

The clinical and pathological features of the first three patients are similar to those described by Evans (1949) and thus are probable examples of familial cardiomegaly, but in none of the three was there any positive family history: such cases, however, can occur sporadically and *de novo* as in the four isolated cases in Evans' series. In addition to the myocardial and endocardial fibrosis in Case 4 there was evidence of a more active process as was shown by the cellular infiltration. The ætiology in all these cases remains obscure, even if it be similar in all. It is doubtful whether the small right coronary artery noted in Cases 1 and 2 is of any significance, but it is of interest that Campbell and Turner-Warwick (1956) in a description of familial cases, similar otherwise to the present series, noted that the coronary arteries were small as compared with the greatly hypertrophied left ventricle in their two patients that came to necropsy. It is possible that a virus, as

yet unidentified, will eventually be found to be the infective agent responsible for these obscure cases of cardiopathy.

Summary

The clinical features of four cases that presented with cardiac hypertrophy and heart failure, but without the signs of the more common forms of heart disease, are described. In each the basic pathological lesion was a myocarditis with a fibrotic reaction in the myocardium.

My thanks are due to Dr. William Evans for his advice, and also to Professor H. Scarborough for his permission to publish Case 3.

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DIFFUSE ENDOMYOCARDIAL SCLEROSIS

BY

J. B. LYNCH AND J. WATT

From the Department of Pathology, University of Liverpool

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In recent years increasing attention has been focused upon a group of cases of congestive cardiac failure that present a distinctive cardiac morphology. There is diffuse thickening of the mural endocardium of one or both ventricles and fibrosis of the myocardium which is largely confined to the inner third of the ventricular wall; the coronary arteries are normal or show minimal arteriosclerosis. Since little is known of the pathogenesis, and the morphology of the lesion is somewhat variable, we have used the general term " diffuse endomyocardial sclerosis ".

From Europe, particularly Switzerland, there have been several reports of endomyocardial sclerosis, but usually of single cases only. Loeffler (1936) described two under the term " endocarditis parietalis fibroplastica with eosinophilia ", and similar single case reports are those of Mumme (1940), Roulet (1944), Berblinger (1948), Lenègre and Gerbaux (1952) and others. Prior to 1948, only 22 cases had been recorded (Loeffler, 1946–47). Similarly, from America there have been very few examples described (Smith and Furth, 1943; McKusick and Cochran, 1952; McNichol *et al.*, 1953; and others). We have found only two relevant British case reports (Edge, 1946; and Lennox, 1948). A closely similar condition occurring in Africa is endomyocardial fibrosis: several detailed clinical and pathological studies on a large number of these cases have been made and Davies and Ball (1955) note that it was responsible for 33 of the 231 deaths in Uganda from cardiac failure in the period 1951–53. This curious anomaly of the geographical incidence of the condition remains unexplained.

A lesion morphologically allied to endomyocardial sclerosis occurs in infants, and has been described as fœtal endomyocarditis (Farber and Hubbard, 1933), endocardial dysplasia (Prior and Wyatt, 1950), and congenital fibroelastosis (Gowing, 1953). The relationship of this condition to that in the adult remains *sub judice* at present.

We have collected four adult cases of diffuse endomyocardial sclerosis during the past four years and it is possible that the condition in this country, though rare, may escape notice. Material from cases of endomyocardial sclerosis occurring in African natives and from cases of congenital fibroelastosis in infancy has been studied for comparison. A composite clinical and pathological picture of diffuse endomyocardial sclerosis will be given and only a brief résumé of each case is presented.

Case Summaries

Case 1. A Jewess, aged 51 years, suffered from recurrent attacks of asthma sometimes with præcordial pain, for six months before admission to hospital. On examination the essential findings were diffuse bronchial spasm, a mild degree of hypertension (B.P. 170/100), and eosinophilia. The total white cell count varied from 8000 to 18,000 per c.mm., the eosinophilia fluctuating within the range 4 to 31 per cent. Her death was sudden and unexpected and was presumed to be the result of acute coronary ischæmia.

Post mortem there was a diffuse vesicular emphysema of the lungs and a moderate degree of chronic venous congestion of the abdominal viscera. The heart was enlarged, weighing 400 g. In the left ventricle there was an extensive endomural thrombus overlying a grossly thickened endocardium (Fig. 1). On histological examination the thickened endocardium consisted of granulation tissue showing numerous capillaries and a diffuse cellular infiltration comprising eosinophil leucocytes, plasma cells, lymphocytes,

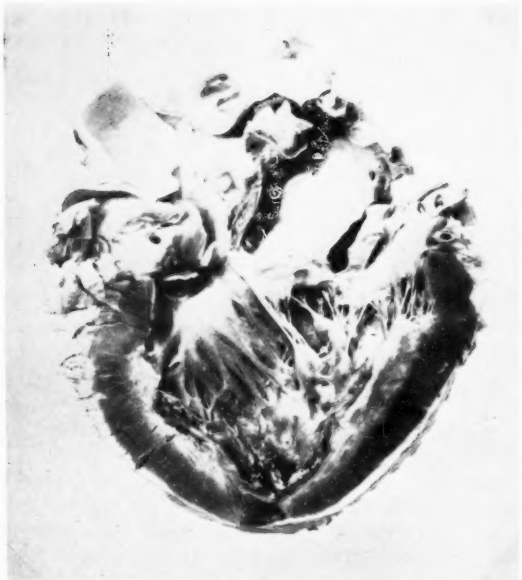

FIG. 1.—Left ventricle, showing endomyocardial sclerosis, apical thrombus, and patent coronary arteries. Case 1.

FIG. 2.—Gross endocardial thickening in the apical region of the right ventricle; hypertrophy of the myocardium. Case 4.

and some hæmosiderin-laden macrophages. There was organization of the deeper layers of the overlying thrombus. The inner elastic lamina of the endocardium lying deep to the granulation tissue showed focal areas of reduplication. There were foci of fibrosis in the myocardium, almost confined to the inner third and sometimes continuous with the overlying endocardium. A scanty infiltrate of lymphocytes and plasma cells was present in several of these foci and also varying degrees of atrophy of the immediately adjacent myocardium. Occasionally there were broad connective tissue septa containing numerous sinusoidal channels. These septa were continuous with the granulation tissue of the thickened endocardium and extended inwards into the myocardium for a variable distance. Arterioles in the subendocardial region showed reduplication of the internal elastic lamina and subintimal fibrosis.

Comment. Initially this case was thought to be one of myocardial infarction with overlying thrombus. However, the coronary arteries were fully patent and showed little or no atheroma, the myocardial fibrosis was focal and limited to the inner third of the ventricular wall, and the endomyocardial sclerosis had not the distribution commonly seen in myocardial infarction.

Loeffler (1936) described two cases characterized by a progressive cardiac failure, eosinophilia, and diffuse thickening of the mural ventricular endocardium. Writing in 1947 he stated "the diagnostic clinical aspect of this condition is quite clear; it is the aspect of the so-called Fridl-Pick type of general central stasis, with this important difference that the pericardium in my cases proves to be absolutely free." It would appear that this syndrome is composed of the following triad; a clinical picture simulating constrictive pericarditis, eosinophilia, and endomyocardial sclerosis, but not all the reported cases have satisfied these criteria. If the endomyocardial sclerosis is severe, affecting the right ventricle or both ventricles, the clinical picture does closely simulate that of constrictive pericarditis (Loeffler, Case 1, 1936; Mumme, 1940; Fossel, Case 1, 1942). McKusick and Cochran (1952) were so impressed by this resemblance that they described a case under the title constrictive endocarditis. In contrast, when the lesion involves only the left ventricle, the differential diagnosis from constrictive pericarditis is not seriously in question (Buchler, 1941–42; Fossel, Case 2, 1942; Berblinger, 1948). Eosinophilia is also inconstant and Egger (1944) thought it was not an obligatory sign: to explain this Loeffler (1947) suggested that it was a phasic phenomenon related to the stage of the disease process at the time of observation. Finally, the most constant component of the triad, the endomyocardial sclerosis, also is variable in site, depth, and extent. There must, therefore, be some latitude in the identification of a particular case as an example of the syndrome.

In this patient the clinical picture of constrictive pericarditis was not present, but the findings of eosinophilia, endomyocardial sclerosis, and the morphological features of early congestive cardiac failure, we believe, warrant its inclusion as an early example of Loeffler's endocarditis syndrome.

Case 2. The essential clinical feature in this woman, aged 36, was a remittent progressive congestive cardiac failure of obscure ætiology and of three years' duration. Previous illnesses included paratyphoid and a tuberculide skin rash. On examination there was gross cardiac enlargement, and a localized soft systolic murmur at the apex. The blood pressure was 110/80; there was no anæmia or eosinophilia. Constrictive pericarditis, possibly tuberculous in origin, was considered but rejected as unlikely, and she was finally thought to have idiopathic hypertrophy of the heart.

The principal autopsy findings were cardiac enlargement (heart weight 630 g.), infarcts in the lung and spleen, œdema, ascites, and chronic passive venous congestion of the viscera. As in Case 1 there was endomural thrombus and thickening of the endocardium affecting the apex, lateral, and posterior walls of the left ventricle. The histology of the endocardium is illustrated in Fig. 3. There was a minimal fibrosis of the myocardium consisting of small finger-like extensions into the subendocardial zone, with only very occasional small foci elsewhere.

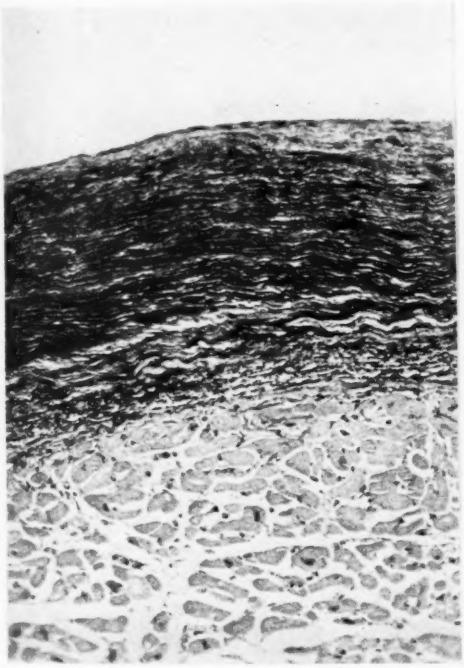

FIG. 3.—Uniform fibro-elastic thickening of the endocardium. Weigert's elastic and van Gieson; × 120. Case 2.

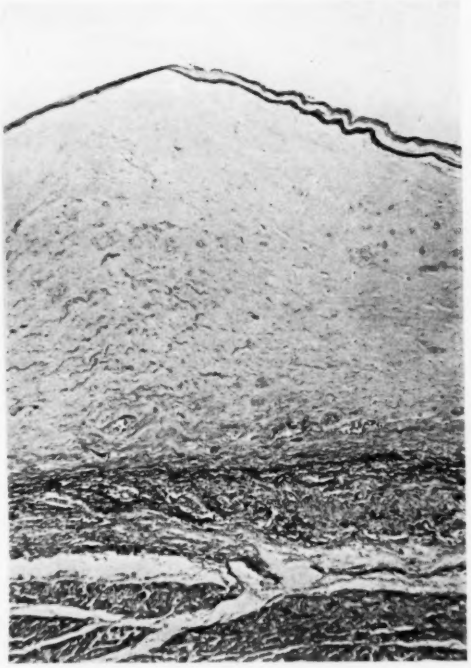

FIG. 4.—Thickened endocardium, showing fibro-hyaline connective tissue with scanty elastic elements. Weigert's elastic, and hæmatoxylin and eosin; × 60. Case 4.

Comment. Several reported cases of idiopathic cardiac hypertrophy show features similar to those found in endomyocardial sclerosis. Thus, in the endocardium small areas of necrosis, fibrinoid degeneration, an acute inflammatory infiltration, and also thickening have been reported (Norris and Pote, 1946). In the myocardium the fibrosis, though usually diffuse, may be mainly in the subendocardial region and indeed, may be restricted to this site (Reisinger and Blumenthal, 1941). In reviewing the pathology of idiopathic cardiac hypertrophy, Fowler (1947) commented on the frequent occurrence of fibro-elastic proliferation of the subendocardium, often associated with thrombus. Finally, the first case in the report of Levy and Rousselot (1933) closely simulates in its description the appearances of endomyocardial sclerosis. As we do not know the pathology of its early stages it is difficult to evaluate its relationship to these cases, especially where the idiopathic cardiac hypertrophy is associated with organizing endomural thrombus (Levy and von Glahn, 1937). To classify certain of these cases as examples of endomyocardial sclerosis is merely to change the name, and requires only a shift in the emphasis from one macroscopic

feature, hypertrophy, to another, endocardial thickening, without in any way increasing our understanding of the underlying disease process.

In the present case the uniform admixture of fibrous and elastic tissue elements of the thickened endocardium and the minimal amount of myocardial fibrosis are of interest in that these morphological features are essentially those found in congenital fibroelastosis. The possible relationship of adult endomyocardial sclerosis to fibroelastosis of infancy will be discussed later.

Case 3. A man, aged 37, suffered from an attack of diarrhœa during a dysentery epidemic while in a Polish concentration camp in 1940. Until his death in 1952, he was subject to several recurrences, each lasting a few weeks. On these occasions blood was present in the fæces, but there was no evidence of a dysenteric infection, bacillary or amœbic. With each attack a severe deficiency state, and gross anæmia developed (red cell count 1·85 million per c.mm.; hæmoglobin 7·4 g. per 100 ml.) though in the interim periods his general health remained fair; therapy included a diet supplemented with vitamins and the anæmia responded to proteolysed liver extracts and folic acid. In his final illness the major clinical features were wasting, anæmia, œdema, ascites, enlargement of the liver and spleen, and a generalized brownish pigmentation of the skin, the latter having been present since 1948. In the differential diagnosis, sprue, Addison's disease and hæmochromatosis were considered, but no decision was reached.

Post mortem, there was atrophy of the gastro-intestinal tract; the adrenals were small but within normal limits; the liver and spleen were enlarged and congested. The heart was small, there was much thickening of the endocardium, similar in distribution to the previous cases, but without overlying thrombus. The mitral valve cusps were slightly thickened and there was a mild degree of stenosis. The thickening of the mural endocardium was not continuous with that of the valve cusps. Microscopically, the thickening consisted of relatively acellular fibro-elastic tissue with several small foci of hyaline degeneration. There was a focal myocardial fibrosis but a striking feature was a continuous zone of fibrosis immediately beneath the thickened endocardium (Fig. 5).

FIG. 5.—Thickening of the endocardium associated with much subendocardial fibrosis. Weigert's elastic, and hæmatoxylin and eosin; × 4. Case 3.

Comment. A primary cardiac disorder was not suspected and in retrospect the role played by the heart in the production of the symptom complex is difficult to evaluate. The possible ætiological relationship of malnutrition, especially vitamin B deficiency, and the cardiac pathology will be discussed in more detail with the next case.

Case 4. A woman, aged 45, enjoyed good health before detention in a Japanese prisoner-of-war camp where in 1942 she developed œdema and ascites: a diagnosis of vitamin B deficiency was made. On her return to England in 1945 she complained of dyspnœa and swelling of the legs. In 1946 she had pleurisy,

in 1950 amœbic dysentery, and in 1951 pneumonia. Thereafter her symptoms steadily increased in severity, and in 1952 there was a loud systolic murmur in the mitral area and a diagnosis of constrictive pericarditis was made. Finally, in 1955 she died a few hours after surgical intervention to relieve the constrictive pericarditis.

Post mortem, there was a moderate degree of cirrhosis of the liver, ascites, and gall stones. The heart weighed 480 g. and showed endomyocardial sclerosis involving both ventricles (Fig. 2 and 6). The histological appearance of the thickened endocardium is shown in Fig. 4. Fibrosis of the myocardium was minimal in the outer two-thirds of the ventricular walls, but in the inner third, sometimes in continuity with the endocardium, there were several focal areas of fibrosis.

FIG. 6.—Diffuse endomyocardial sclerosis of the left ventricle. Note the involvement of the posterior wall behind the mitral cusp, and shortening of the chordæ tendinæ of the posterior leaf. Case 4.

Comment. There is evidence for the thesis that malnutrition and vitamin B deficiency may, on occasion, play a part in the production of endomyocardial sclerosis. The clinical syndrome of heart failure as seen in beri-beri was first discussed by Aalsmeer and Wenckebach (1929), and subsequently by others (Keefer, 1930; Weiss and Wilkins, 1937). Gillanders (1951), however, stressed the variability of the cardiac beriberi syndrome and cast doubt upon its specificity. The morphological findings in the heart are hypertrophy and dilatation of the ventricles associated with hydropic degeneration and interstitial œdema of the myocardium. These changes in chronic untreated cases may be progressive and irreversible, resulting in fibrosis of the myocardium (Benchimol and Schlesinger, 1951) and could well account for the failure of the clinical response to vitamin B therapy. Similar histological changes have been described in the nutritional heart disease of Bantu natives. Though these changes are not specific, they tend to be greatest in the subendocardial region. Further, in the ventricles of several of these cases, endomural thrombi were present which showed varying degrees of organization (Higginson *et al.*, 1952). According to Davies and Ball (1955) it is possible that these cases of nutritional heart disease represent " severe early manifestations of a process that develops more slowly and silently to severe fibrosis in Uganda-Africans." Finally, malnutrition or vitamin B deficiency were considered the possible ætiological factors in three cases of endomyocardial sclerosis described by Smith and Furth (1943). In Cases 3 and 4 of the present series, the history of the onset of symptoms during a period of malnutrition and their persistence for many years supports this hypothesis.

The adhesive pericarditis present in Case 4 was inadequate to explain the clinical features. This confirmed the opinion of the surgeon that a pericardiectomy would afford little relief for the patient. A clinical

picture closely resembling constrictive pericarditis has been reported in several cases of endomyocardial sclerosis in which the pericardium was normal (see Case 1) and the cardiac dysfunction has been attributed to the fibrosis of the endocardium (Loeffler, 1936; and others), for as pointed out by Gunnar *et al.* (1955), any lesion in any layer of the heart causing interference with diastolic expansion may simulate in its effects the clinical syndrome of constrictive pericarditis.

Pathology and Clinical Features of Endomyocardial Sclerosis

Satisfactory definition of endomyocardial sclerosis as a clinicopathological entity is difficult for little is known of its proximate causation. Early examples may pass unrecognized since varying degrees of thickening of the mural endocardium, both focal and diffuse, are not uncommonly found at autopsy as an incidental finding in a variety of conditions, or in association with chronic myocardial infarction, intraventricular thrombus, syphilis, chronic dilatation of the heart, and scleroderma (Norris, 1937; Weiss *et al.*, 1943; Flynn and Mann, 1946; Becker *et al.*, 1953). At present therefore only the terminal and severe phases of endomyocardial sclerosis can be identified with any degree of certainty.

Pathology. In most cases the heart is enlarged with dilatation and hypertrophy of one or more chambers. The heart weights recorded have ranged from 300g. to 759g. There are no pronounced changes in the atria although occasionally endocardial thickening is described and thrombus may be present. The striking feature is the pearly white rugose thickening (1–4 mm.) of the ventricular endocardium. The pattern of distribution appears fairly constant: the thickening involves the trabeculated surface of the ventricles, rarely if ever affecting the smooth surface of the interventricular septum below the aortic and pulmonary valves, and the most constant site is the apex of one or both ventricles, more commonly the left, with a predilection for extension up the posterior wall. Significant lesions of the valves are not a feature though the mitral valve may show moderate degrees of scarring and/or mild stenosis. The chordæ tendineæ may be thickened, fused and shortened, and occasionally bound down to the posterior wall of the ventricle, and this occurs more commonly in relation to the chordæ of the posterior mitral cusp (Fienberg and Holzman, 1951; Case 4). Vegetations on the valves have been described but are rare (Mumme, 1940). Overlying the thickened endocardium varying amounts of thrombus are common, sometimes almost entirely filling the ventricles (Roulet, 1944; Egger, 1944). A focal and linear fibrosis of the myocardium is observed macroscopically but is usually minimal in degree. The pericardium is normal and commonly a moderate effusion is present. The coronary arteries are fully patent though a little atheroma may sometimes occur.

On microscopic examination the thickened endocardium is composed of fibrous tissue with areas of hyaline degeneration. Though elastic tissue fibrils are present, they are few in number and have no regular arrangement; focal areas of reduplication are sometimes seen. In the deeper aspect, there is a loose connective tissue often containing numerous thin-walled blood vessels and a scanty focal lymphocytic infiltration. In the myocardium there is focal fibrosis, mainly of the inner third, sometimes with a slight cellular infiltrate. In addition large tongue-shaped septa of fibrous connective tissue containing small sinusoidal vessels extend from the endocardium into the myocardium. Commonly, there are variable degrees of thickening of the walls of the small arteries and arterioles in the subendocardial zone. The histological features are those of a lesion in the chronic healed phase.

Clinical Features. Most cases of endomyocardial sclerosis occur in the third and fourth decades. There is no significant preponderance of either sex. There are no relevant findings in the family history, and no example of endomyocardial sclerosis in siblings has been recorded, although Smith and Furth (1943) mention that a sister of one of their patients died suddenly from " myocarditis " at the age of 22 years. Cases of endomyocardial sclerosis have been reported from several countries, the majority from Switzerland, but this may possibly be explained by the increased awareness of the condition in certain localities.

Although in some cases there are references to gastro-intestinal disorders, dietary insufficiency, syphilis, diphtheria, and respiratory tract infections (Case 2 and 3; Hübschmann, 1917; Levy and

Rousselot, 1933; Fossel, 1942; and others) the previous medical history is of little diagnostic value. The duration of the disease is very variable ranging from sudden and unexpected death to a history extending over ten years or more (Landau *et al.*, 1927; Comeau, 1937; Smith and Furth, 1943). Clinical assessment of the duration of the cardiac lesions must be largely guess-work, for the symptoms of the initial phases are not known—a difficulty illustrated by our Cases 1 and 3. One patient had been passed as fit for military service with a normal X-ray of the chest five years before death (Hoffman *et al.*, 1955).

Although diffuse endomyocardial sclerosis may be an unexpected finding at autopsy (Case 1), the common clinical picture is one of cardiac failure which may be predominantly right or left-sided in type. The failure may last only a few weeks, or for some years with a remittent though steadily progressive course. Not infrequently the clinical features are suggestive of constrictive pericarditis (Loeffler, 1936; Egger, 1944; and others), and indeed so close is the similarity that operation for the relief of constrictive pericarditis has on occasion been performed.

Certain symptoms and signs are considered from the diagnostic standpoint. As would be expected from the morphological finding of normal coronary arteries, the striking feature of the group as a whole is the absence of anginal pain. Occasional cases are reported with pain in the chest of possible cardiac origin (Case 1; Baumler, 1911; Loeffler, 1936) and in one case a clinical diagnosis of coronary embolism was made (Berblinger, 1948). The clinical course is afebrile; where there is a raised temperature, the cause is fairly obvious, e.g. respiratory infection, pulmonary infarction, etc. and unexplained pyrexia is rare (Buchler, 1941–42).

Although on clinical and radiographic examination the *heart* usually shows some enlargement, it may be of normal size (Case 3; Loeffler, 1936; McKusick and Cochran, 1952). There are no constant auscultatory findings in endomyocardial sclerosis, but in the severe cases when the mitral valve is sclerotic, there is commonly a loud apical systolic murmur (Case 4; Loeffler, 1936; Mumme, 1940; Fienberg and Holzman, 1951). Hypertension is rare at any time during the course of the illness, but a mild degree has been recorded (Case 1; Mumme, 1940; Berblinger, 1948).

The changes recorded in the *electrocardiogram* are non-specific and include sinus tachycardia, left axis deviation, flat or inverted T waves, and some widening of the QRS complex. In Case 4 there was RS–T depression in leads V1 and V2, V5 and V6 and RS–T elevation in aVR which may be interpreted as indicating predominant subendocardial damage, but other factors, e.g. digitalis may have been responsible. The changes of bundle-branch block have been recorded (Comeau, 1937; Toreson, 1944).

A mild or moderate degree of hypochromic *anæmia* is usually present. However, the red blood cell picture may be normal (Case 1; Deus, 1916) or there may be a very severe anæmia (Case 3; Buchler, 1941–42). The blood sedimentation rate may be within normal limits or may be increased; a moderate leucocytosis is not infrequent and with a raised sedimentation rate has been considered to support an infective origin (Jucker, 1946). Eosinophilia is a valuable diagnostic feature but it is not always present. It varies in degree not only from case to case but even in the same case (4 to 63 per cent Mumme, 1940; 50 to 58 per cent Roulet, 1944; 15 per cent Egger, 1944; 5 per cent Berblinger, 1948; and absent McNichol *et al.*, 1953). Apart from lung infarctions, *embolic phenomena* in other viscera are not so common as one might expect in view of the frequency of endomural thrombus. Infarctions in the kidney have been described by Smith and Furth (1943), and in the spleen by Hoffman *et al.* (1955).

Endomyocardial Fibrosis in Africa

This is not uncommon in the natives of certain parts of Africa. Since it was reported by Bedford and Konstam (1946) there have been several accounts of large numbers of cases with full clinical and pathological details particularly in Uganda (Davies, 1948; Ball *et al.*, 1954; Williams *et al.*, 1954; Davies and Ball, 1955) and in the Sudan (O'Brien, 1954) and in Europeans who have lived in Africa (Gray, 1951).

The clinical picture is very similar to that of endomyocardial sclerosis: a young or middle-aged adult of either sex suffers from progressive congestive heart failure of variable duration, without evidence of any of the more common causes of failure. The endocardial sclerosis may involve the mitral or tricuspid valves and cause incompetence, and when the mitral valve is affected an important diagnostic feature is a loud, high-pitched apical systolic murmur. Occasionally a syndrome simulating constrictive pericarditis occurs. The electrocardiogram is of little assistance and shows no constant pattern. Among Africans the importance that can be attached to eosinophilia is reduced in view of the frequency of parasitic infestation.

The similarity of the macroscopic appearances of the two conditions is very striking and such differences as exist are probably only those of degree. In the African series the incidence of mural thrombus and cardiac hypertrophy is lower, the sclerotic process more frequently involves the right ventricle, the mitral and the tricuspid valves, and calcification of the endocardium is more common. The histological picture is " extremely uniform despite variations in the gross appearances " (Davies and Ball, 1955). It is one of fibro-hyaline thickening of the endocardium with small amounts of elastic tissue, a deep zone with numerous small, thin-walled vessels and a septal and focal myocardial fibrosis mainly of the inner third. We received from Professor Williams of Makerere College, Uganda, for comparison with our own material, representative blocks of tissue from three typical cases of " endomyocardial fibrosis ", and the histological features were very similar to those of our Case 4.

Although it is difficult to establish the identity of African and non-African cases it does appear from the present study that the clinical and morphological findings are essentially the same in the two groups.

Congenital Fibroelastosis: its Relationship to Endomyocardial Sclerosis

Congenital fibro-elastosis has become a well-recognized cause of death in infancy. The gross pathological findings bear some resemblance to adult endomyocardial sclerosis and for comparison we have studied ten cases.

Serious congenital anomalies of the heart were found in three cases, all infants below the age of three months, viz. a single atrium and single ventricle with a common truncus arteriosus, a rudimentary left ventricle with severe aortic stenosis, and a patent ductus arteriosus with undifferentiated aortic valve cusps. In all the hearts there was a diffuse fairly uniform, greyish-white thickening of the mural endocardium of the left ventricle (Fig. 7). A similar thickening was observed in the left atrium in one heart, and in the right ventricle in another. Ante-mortem thrombus was present in the left ventricles in two cases. There were no abnormalities of the pericardium or coronary arteries.

Major points for comparison and distinction of congenital fibroelastosis and adult endomyocardial sclerosis will be considered.

Age and Sex. A cardinal difference is of course the age incidence. In a review of 98 cases of congenital fibroelastosis, Lambert *et al.* (1953) found that 96 per cent died in the first year of life. In the present series, only one infant survived beyond that period. Of particular interest, however, are the cases recorded in children at 5, 6, and 11 years of age (Kugel and Stoloff, 1933; Dennis *et al.*, 1953), and in young adults (Toreson, 1944; Thomas *et al.*, 1954). These cases support the possibility that rarely, adult endomyocardial sclerosis may result from the persistence of congenital fibroelastosis into adult life. Occasionally congenital fibroelastosis has been reported in siblings (Ullrich, 1938; Weinberg and Himmelfarb, 1943; Greaves *et al.*, 1954); there has been no such report in adult endomyocardial sclerosis.

Heart. There are often discrepancies in the recorded incidence of heart murmurs and of heart size in congenital fibroelastosis (Adams and Katz, 1952; Lambert *et al.*, 1953). Thus, Dennis *et al.* (1953) say that enlargement of the heart is rare, while Mortensen *et al.* (1954) say that it is present in 94 per cent of cases. In adult endomyocardial sclerosis heart murmurs may or may not be heard and the size of the heart is variable and not always enlarged.

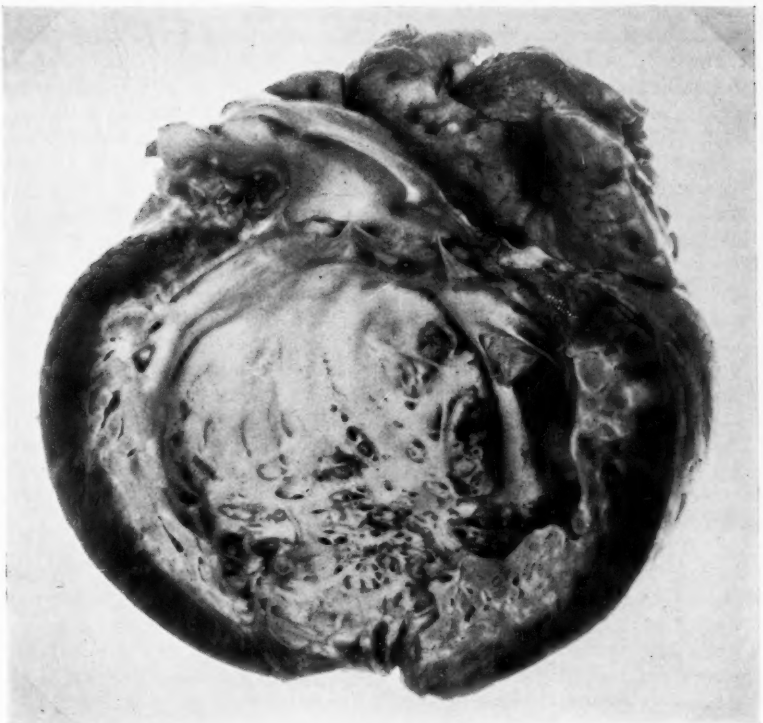

FIG. 7.—Congenital fibro-elastosis in a female infant, aged 13 weeks.

The electrocardiograms do not reveal a constant pattern of diagnostic value in either group although they may be of some value in the differential diagnosis of congenital fibroelastosis (Vlad *et al.*, 1955). Common abnormalities are left axis deviation, alteration of the P wave, and abnormalities of the T wave, usually depression. Bundle-branch block is occasionally observed; it is more common in congenital fibroelastosis. Rarely, complete heart block has been recorded in the infant, but not in adult endomyocardial sclerosis (Stadler *et al.*, 1950).

Course of the Disease and the Diagnosis. In both groups the terminal illness may be very short or may be preceded by recurrent episodes of cardiac failure. At present the diagnosis in either group is largely one of exclusion, although more recently in congenital fibroelastosis with the aid of angiographic studies, the clinical diagnosis has been made with sufficient confidence to carry out surgical treatment (Paul and Robbins, 1955). We have found no reference to eosinophilia in congenital fibroelastosis, a finding in contrast to adult endomyocardial sclerosis.

Morphology. The essential features common to both conditions are the mural thickening of the endocardium of one or both ventricles, usually the left; normal coronary arteries (except those cases of congenital fibroelastosis associated with an aberrant left coronary artery); variable though minor degrees of fibrosis of the myocardium, and no significant lesions of the pericardium. However, there are certain important differences. In the congenital group the thickening is smooth, more uniform, and more diffuse, usually involving all the mural endocardium of the left ventricle. The " outflow tract " is the commonest site and the thickening is frequently most pronounced just below the aortic valve. In contrast, in the adult case, the affected site is almost always part of the

trabeculated area of the left or right ventricle, particularly the apex. The smooth sub-aortic region of the interventricular septum is rarely if ever involved, despite the fact that focal areas of endocardial thickening occur quite frequently at this site. In the congenital group, the incidence and degree of thrombus formation is much less than in the adult group. In the infant, congenital anomalies of the heart are frequently present, e.g. stenosis or atresia of the aortic or mitral valves, coarctation of the aorta, left ventricular hypoplasia, etc.; in the adult, they are very rare, although aortic hypoplasia has been described (Bedford and Konstam, 1946). The incidence and type of valve lesion differ appreciably in the two groups. In congenital fibroelastosis, the most common lesions are those of the aortic valve. In adult endomyocardial sclerosis the most frequent finding is one of direct involvement of the posterior leaf of the mitral valve or its chordæ tendineæ by spread of the sclerotic process from the endocardium; significant lesions of the aortic valve rarely if ever occur. However, as Horley (1955) has pointed out, and as confirmed in the present series, there is a broad subdivision of congenital fibroelastosis into two groups, viz. fœtal and infantile. In contrast to the fœtal variety, the infantile group includes those cases that survive beyond three months and do not have associated congenital anomalies. A certain proportion of such cases persist into childhood, and it is possible therefore that on occasion they may reach adult life (Thomas *et al.*, 1954; Panke and Rottino, 1955). Support for this hypothesis is found in the histological features of certain cases of adult endomyocardial sclerosis in which the thickened endocardium shows a uniform admixture of elastic and fibrous tissue elements as found in congenital fibroelastosis. However, this histological pattern is uncommon in adult endomyocardial sclerosis, in most cases of which fibro-hyaline connective tissue is the major component of the endocardial thickening and elastic elements are only slight in amount and not uniform in distribution. Further, in Case 2 of the present series, while the histological features conform to those of congenital fibroelastosis, the macroscopic distribution of the lesion is that of adult endomyocardial sclerosis. Finally, in the usual adult case the myocardial fibrosis is more severe and is not confined as in the infant to the immediate subendocardial region. With the possible exception of rare examples of congenital fibroelastosis persisting into adult life, it would appear therefore, that adult endomyocardial sclerosis and congenital fibroelastosis should be considered as separate entities.

Ætiology and Pathogenesis of Adult Endomyocardial Sclerosis

Both the endocardium and the myocardium have been suggested as the initial site of the lesion in endomyocardial sclerosis. The consensus of opinion is that the myocardium is the primary site and that the diffuse endocardial thickening is secondary, resulting probably from organization of an endomural thrombus. The morphological evidence favours the latter. Support for the theory that " organized thrombus " is largely responsible for the endocardial thickening is to be found first, in the localization of the lesion to the trabeculated areas of the ventricles where mechanical factors (eddies, etc.) would predispose to the formation of thrombus, secondly, in the histological features such as areas of hyalinization and the deep vascular zone of the thickened endocardium, and thirdly, in the frequent occurrence of endomural thrombus.

In the past, individual authors on the basis of a single or very small series of cases, have sought to establish a particular concept with the result that several theories have been formulated as to the ætiological factor concerned. In the present four cases, the clinical evidence could be offered in support of different ætiological factors, e.g. allergy (Case 1), or malnutrition and vitamin B deficiency (Cases 3 and 4).

An allergic basis for the lesion is suggested by the frequent occurrence of eosinophilia (Loeffler, 1946–47) and by those cases with clinical evidence of an allergic or hyperergic state, e.g. severe urticaria (Buchler, 1941–42), rheumatoid arthritis (Egger, 1944), periarteritis nodosa (Roulet, 1944; Watt and Lynch, 1956) and asthma (Lennox, 1948; Case 1). However, eosinophilia is not a constant finding and the incidence of allergic or hyperergic states is insufficient to permit their consideration as the sole pathogenic factor.

The role of malnutrition and vitamin B deficiency in the ætiology of endomyocardial sclerosis

has been discussed (Case 4). Although malnutrition is common in Africa and may be important in African cases, the absence of dietary insufficiency in many of the patients in other countries precludes the hypothesis from explaining all examples of endomyocardial sclerosis.

In view of the frequency of gross endocardial thickening and fibrosis of the myocardium in chronic infarction, the possible role of coronary ischæmia must be considered in the ætiology of endomyocardial sclerosis. On clinical and morphological grounds most chronic myocardial infarcts are readily differentiated but the rare case of subendocardial infarction closely resembles endomyocardial sclerosis (Hughes and Smith, 1953). The state of the coronary vessels will usually identify such a case, but the occurrence of subendocardial necrosis where the coronary vessels are either normal or show minimal disease is of interest. The necrosis has been attributed to relative ischæmia of the subendocardial zone caused by a variety of factors, e.g. systemic shock, chronic anæmia, cardiac hypertrophy, etc. (Master *et al.*, 1949; Horn *et al.*, 1950; and Levine and Ford, 1951). Although the electrocardiographic findings are different in the two conditions certain examples of endomyocardial sclerosis may represent a healed phase of subendocardial necrosis, particularly if this has been associated with endomural thrombus.

Clinical and morphological features closely similar to those of endomyocardial sclerosis are found in idiopathic forms of myocarditis associated with endomural thrombus, and such cases have been reported from other countries as well as from Africa (Roque and Levy, 1914; von Bonsdorff, 1939; Dammin *et al.*, 1951). Finally there are several possible or indeed probable examples of endomyocardial sclerosis reported as some form of myocarditis, e.g. primary subacute myocarditis (Josserand and Gallavardin, 1901; Gallavardin and Gravier, 1929) myocarditis perniciosa (Boikan, 1931), diffuse isolated myocarditis (Toreson, 1944) and chronic fibroplastic myocarditis (Ware and Chapman, 1947). In the toxic form of myocarditis that follows the administration of organic arsenicals, Brown and McNamara (1940), and Taussig and Oppenheimer (1936), have described damage to the endocardium, and indeed, a typical case of endomyocardial sclerosis was reported by Edge (1946).

No case of endomyocardial sclerosis directly attributable to an inflammatory form of myocarditis has been described. The focal fibrosis of the myocardium and the not infrequent association of a cellular infiltrate which may include lymphocytes, plasma cells, eosinophil leucocytes, and even giant cells (Comeau, 1937) do not necessarily indicate that the myocardial damage has an inflammatory basis. However, in his review of myocarditis Saphir (1941–42) notes that sometimes the endocardium is also involved, e.g. in trichinosis, Rocky Mountain spotted fever, and Libman-Sach's disease. Further, in diphtheria and scarlet fever, associated with an inflammatory infiltration of the endocardium there is a myocarditis in which the lesions are most marked in the subendocardial zone in the walls of the Thebesian vessels, a distribution recalling that of fibrosis in endomyocardial sclerosis. Endocardial thickening may also occur in virus infections, e.g. in rabbits (Pearce, 1954). Again, in discussing syphilis of the myocardium, Norris (1937) states that the endocardium may be white and thickened. Although the association may be fortuitous or due to yaws, a positive Wassermann reaction is not uncommon in African endomyocardial fibrosis, and a myocarditis of obscure origin, possibly syphilitic, also occurs in Uganda (Davies, 1948*a* and *b*).

It appears therefore that endomyocardial sclerosis is a terminal phase of a pathological process that has a multifactorial causation. As in chronic nephritis and cirrhosis of the liver, the identity of morphology of this terminal phase does not necessarily imply a unity of pathogenesis in all cases.

Summary

The clinical and pathological features of four cases of diffuse endomyocardial sclerosis are described. In each there was fibrosis of the myocardium particularly in the inner third, much thickening of the endocardium, and little or no evidence of coronary arterial disease.

Clinically, endomyocardial sclerosis usually presents as a case of cardiac failure of obscure origin. Occasionally it may simulate the syndrome of constrictive paricarditis. Of assistance

in the diagnosis is the presence of eosinophilia, or incompetence of the mitral or tricuspid valves. Electrocardiographic changes are non-specific.

The morphological findings were compared with those in three cases of African endomyocardial fibrosis and ten cases of congenital fibroelastosis in infancy. The pathology of our four cases and that of the African material is essentially similar. Although it is possible that congenital fibroelastosis may persist into adult life and simulate endomyocardial sclerosis, it differs in its distribution and histology and must be considered a separate entity.

The hypothesis is advanced that diffuse endomyocardial sclerosis represents the terminal phase of various disease states, each of which affects a particular site, viz. the innermost layer of the myocardium. As exemplified in this small group of cases, two important factors in the pathogenesis of the condition are malnutrition and allergy.

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FIBRO-ELASTOSIS OF THE HEART IN ADOLESCENCE

BY

W. H. R. AULD AND HAMISH WATSON

From the Department of Pathology, University of Aberdeen, and the Department of Medicine, University of St. Andrews

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Heart failure in young subjects, when unaccompanied by signs of congenital abnormality or rheumatic disease, can pose a diagnostic problem that may remain unsolved even after careful pathological study. A proportion of such cases in infancy is caused by endocardial fibro-elastosis (Prior and Wyatt, 1950; Dennis *et al.*, 1953), and it has even been suggested that this is one of the commonest types of fatal heart disease in the first year of life (Blumberg and Lyon, 1952). Diagnosis during life is often difficult and the possibility of survival into late childhood or adolescence must be considered when any case of heart disease of unknown ætiology is discovered at this age. Gowing (1953) and Elster *et al.* (1955) have both stated that such cases are not to be found, and that their absence in this intermediate age group suggests that the infantile condition is not ætiologically related to any form of idiopathic heart disease in adults. However, Thomas *et al.* (1954) have published a group of five acceptable and uncomplicated cases, ranging in age from 5–16 years, that were pathologically indistinguishable from the infantile form of the disease, and occasional reports of others, probably similar, have appeared during the last fifty years which suggest that, though rare, survival may occur (Table I). It is interesting that the cases described by Thomas *et al.* had all previously been reported as examples of "idiopathic" heart disease.

TABLE I

CASES PRESENTING IN CHILDHOOD AND ADOLESCENCE, SHOWING CARDIAC LESIONS MORPHOLOGICALLY RESEMBLING THOSE OF INFANTILE FIBRO-ELASTOSIS

Author	Age at death	Remarks
	(years)	
Mahon (1936)	2½	
Vulliamy (1947)	2¾	No reference to elastic stains
Michaud (1906)	3	No reference to elastic stains
Thomas *et al.* (1954), Case 5..	5	
Peale and Lucchesi (1942) ..	5	Complicated by measles, encephalitis, and gonococcal pyosalpinx
Thomas *et al.* (1954), Case 6..	6	
Kugel and Stoloff (1933) ..	6	No reference to elastic stains
Thomas *et al.* (1954), Case 7..	7	
Thomas *et al.* (1954), Case 8..	11	
Blumberg and Lyon (1952) ..	11	
Watt and Lynch (1956) ..	12	Associated with periarteritis nodosa: authors do not consider it of congenital origin
Fowler (1947)	14	No reference to elastic stains
Present case	15	
Thomas *et al.* (1954), Case 9..	16	

The following boy with cardiac failure of obscure origin, whose electrocardiogram suggested extensive myocardial infarction, showed at autopsy many of the features of congenital endocardial fibro-elastosis.

Clinical History. A boy of 13 had always appeared healthy. He was the eldest of five brothers and two sisters. He came from a broken home and for three years before admission had been in a residential school for juvenile delinquents, where he seemed fit and able for the rough and tumble of institutional life and organized games.

While playing football he collapsed and was carried off the field. He had felt dizzy just before this, but apart from a few days' constipation had no other complaints. That evening he had vague abdominal pains, and though apyrexial, had several attacks of diarrhœa and vomiting during the night. The following day he developed a mild pyrexia (100° F.), which, with the diarrhœa and vomiting, persisted for four days. He was treated with penicillin by injection and after two weeks was fit to be sent on sick leave. While on holiday a local practitioner suggested a few days' rest in bed and advised him to take things very quietly. On his return to school he looked ill and was tired and listless in spite of long nights in bed. Three days later, whilst trying to run with other boys, he became acutely breathless and dizzy, was admitted to the school sanatorium, and found to be suffering from congestive heart failure, one month after his first collapse.

On admission he was tired and ill, with slight cyanosis, distended neck veins, obvious orthopnœa, and gross pitting œdema of feet, ankles, and shins. There was sinus tachycardia at 108 a minute and the blood pressure was 90/60 mm. Hg. The apex beat, slightly thrusting, was visible in the fifth left interspace half an inch outside the mid-clavicular line. There was gallop rhythm with poor quality heart sounds, a soft apical systolic murmur, and the pulmonary second sound was loud and split. Fine crepitations were present at both lung bases, but there was no enlargement of the liver or spleen and no retinopathy. Heart screening showed generalized cardiac enlargement of moderate degree, and the cardiogram showed an extensive anterior transmural infarct pattern, which from the ST–T wave segments appeared to be in a healing phase (Fig. 1). The most extensive biochemical, bacteriological, and clinico-pathological investigations were carried out and were all normal. No family history of cardiac or other significant illness was obtained. The mother, father, and two siblings were examined fully, and no abnormality was found.

The congestive heart failure responded very slowly to treatment, and after four months in hospital he was discharged on a low salt diet and a maintenance dose of digitalis. Despite greatly restricted activity the congestive failure recurred after three weeks and he was re-admitted to hospital in January, 1954. The clinical picture was much as before, and further investigations threw no new light on the ætiology. A cardiogram showed only minor changes associated with healing of the previously diagnosed infarct (Fig. 1).

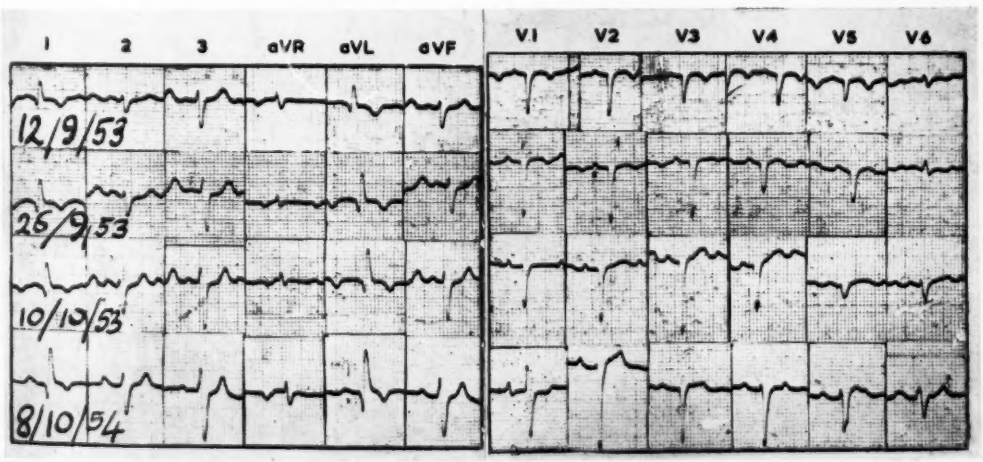

FIG. 1.—Electrocardiograms, showing the pattern of an extensive anterior transmural infarct.

Response to treatment was again slow and a further four months elapsed before he was fit to go back to school. This time, however, he was better than previously and able for moderate activity. He continued on a low salt intake and maintenance dose of digitalis and was seen every two weeks for the next seven months, during which time his condition did not change. In December, 1954, he went to live in another district and one month later his congestive heart failure returned. He was admitted to another hospital in January, 1955, but failed to respond to treatment and gradually deteriorated, dying suddenly two months later.

Necropsy Findings. The main findings were related to the heart. The pericardial sac was healthy. The heart was normal in shape but was considerably enlarged, weighing 525 g. Some patchy areas of pallor were noted in the epicardium on the anterior aspect of the left ventricle. All chambers were dilated especially the left ventricle, the internal measurements of which were $9 \times 7 \times 5$ cm. The left ventricular wall measured 13 mm., the right 7 mm. in thickness. Both atrio-ventricular rings were dilated but the cusps were normal and the pulmonary and aortic valves were healthy. There was no septal abnormality. Pale areas of fibrosis were found throughout the anterior wall of the left ventricle especially in the subendocardial region. The wall was thinned in this part and a large mural thrombus was present over part of the affected area (Fig. 2). Elsewhere the myocardium was of a healthy brown colour. The endocardium in the left ventricle

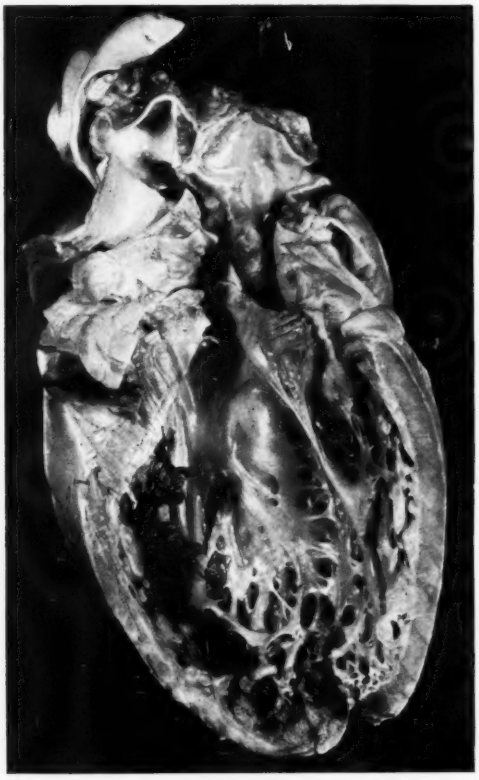

FIG. 2.—The left ventricle viewed from the front. The cut surfaces show the thickened white endocardium with overlying mural thrombus.

was for the most part opaque and white, especially on the anterior and lateral walls of the chamber. The thickened areas merged gradually into normal endocardium at their margins. Similar though slighter endocardial changes were found in the right ventricle, mainly on the septal wall and throughout both atria.

The pulmonary trunk was wider than the aorta, the respective diameters being 20 mm. and 16 mm. Both coronary arteries arose from the aorta, and their ostia were fully patent: the left orifice was elliptical in shape with a mean diameter of 2·5 mm.; the right measured 4·2 mm., and the sum of these diameters was within normal limits. The left coronary artery was of a smaller calibre than the right but both vessels and their main branches were entirely healthy; in particular no atheroma or thrombus formation was demonstrated in a meticulous dissection. Apart from some early atheromatous lesions in its first few centimetres the aorta was of normal appearance. The ductus arteriosus was closed.

Other Findings. Both pleural cavities contained straw-coloured effusions and there was gross ascites. The lungs were firm and congested. The right lower lobe contained three hæmorrhagic infarcts with reddish-brown ante-mortem thrombus in a branch of the pulmonary artery. In the brain a small yellow area of softening about 2 cm. in diameter was present in the cortex of the right parietal lobe. The liver was of normal size but showed nutmeg changes characteristic of chronic venous congestion. The spleen and kidneys were congested in appearance and in the right kidney two small depressed scars resembling healed infarcts were found. There was no evidence of primary renal disease. The left femoral vein was occluded by ante-mortem thrombus.

Histological Findings. A conspicuous abnormality in the wall of the left ventricle took the form of a pronounced fibrous thickening of the endocardium. This extended over much of the interior of the chamber, investing the papillary muscles and sometimes dipping into crypts in the myocardium. Special stains showed that this layer had a rich content of elastic tissue (Fig. 3). Although this fibro-elastic thickening

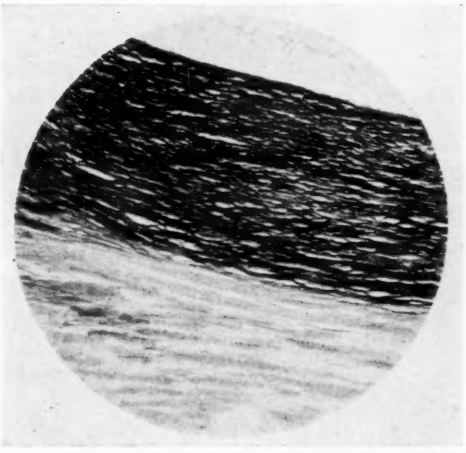

FIG. 3.—Thickened endocardium of the left ventricle, showing proliferation of elastic tissue, with subjacent fibrosis of the myocardium. Orcein, ×55.

was most conspicuous in the left ventricle it was also present to a variable degree in the right ventricle and in both atria. Superficial to the thickened endocardium in the left ventricle the mural thrombus showed varying degrees of organization. In its deeper layers it consisted largely of loose, rather vascular fibro-cellular tissue (Fig. 4).

Numerous zones of interstitial fibrosis, often confluent, were present in the myocardium of the left ventricle. Anteriorly these were scattered throughout the whole thickness of the ventricular wall. In the lateral wall the fibrosis was mainly subendocardial in situation. Similar though less pronounced changes were found in other areas of the heart, notably in the wall of the right atrium and right ventricle (Fig. 5 and 6). Some of these areas of scarring showed a variable admixture with elastic tissue. The muscle fibres, particularly in the neighbourhood of these lesions, were hypertrophied, and often contained large, aberrant hyperchromatic nuclei (Fig. 7). No foci of recent myocardial necrosis were present nor any significant cellular infiltrate in the myocardium. Sections of the heart valves showed no significant abnormality.

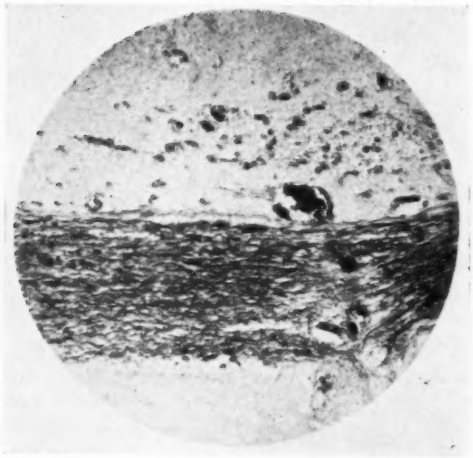

FIG. 4.—Organizing mural thrombus superimposed on fibro-elastosis of the endocardium. Orcein, ×55.

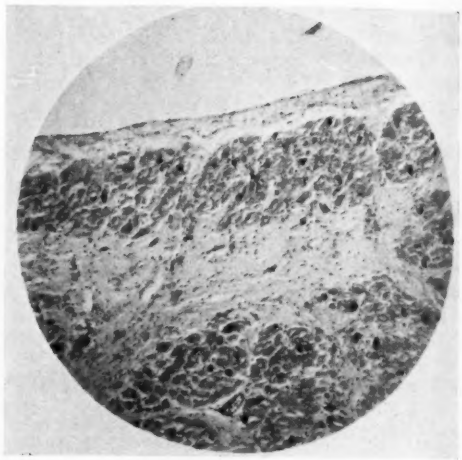

FIG. 5.—Interstitial fibrosis of the myocardium of the right atrium. Hæmatoxylin and eosin, ×55.

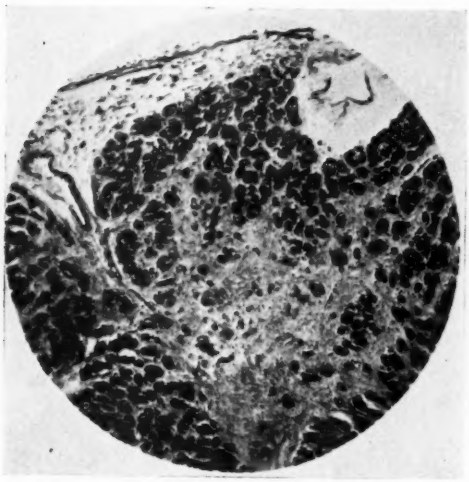

FIG. 6.—Interstitial fibrosis of the myocardium of the right ventricle. Masson's trichome, ×55.

FIG. 7.—Left ventricle. The myocardial fibres are hypertrophied and show large aberrant muclear formations. Hæmatoxylin and eosin, ×240.

The coronary arteries examined at many levels showed no evidence of occlusion. They were indeed entirely healthy in appearance with a single exception of one small arteriole in the wall of the left ventricle which exhibited only a comparatively slight thickening of its intima.

The salient features in other organs were organizing thrombus in branches of the right pulmonary artery with pulmonary infarction; chronic venous congestion of the lungs, liver, spleen, and kidneys; infarcts of considerable duration in the brain and right kidney. Sections from the various organs showed no evidence of any condition belonging to the group of collagen diseases.

Discussion

Cardiac failure of obscure ætiology occurring in young or middle-aged adults, though rare in this country, is not uncommonly reported from America, the European continent, and Africa. If cases showing unexplained inflammatory lesions of the myocardium, as in so-called isolated or Fiedler's myocarditis, are excluded, an apparently miscellaneous group remains in which cardiac hypertrophy has been the common feature. Opinions about ætiology have ranged from dietary deficiencies, antecedent inflammations, etc., to disturbances of collagen metabolism, and the condition has been described by various names (Comeau, 1937; Reisenger and Blumenthal, 1941; Smith and Furth, 1943; Sellars and Phillips, 1946; Ware and Chapman, 1947; Davies *et al.*, 1951; Becker *et al.*, 1953; Thomas *et al.*, 1954; Elster *et al.*, 1955).

This disease group probably includes several distinct syndromes. The endomyocardial fibrosis reported from Africa (Williams *et al.*, 1946) differs in important respects from that seen in America, though a rather similar type has been described in Europe (Löffler, 1936). A few cases, some of sudden death without antecedent illness, probably form another group, in which massive cardiac hypertrophy is the only abnormality (Laubry and Walser, 1925; Whittle, 1929; Reifenstein and Chidsey, 1945). A familial tendency has occasionally been demonstrated (Evans, 1949) and some of these may be related to Friedreich's ataxia. Some can no longer be regarded as idiopathic; examples of glycogen disease affecting the heart have been included in earlier series (Levy and von Glahn, 1944), and mention of coronary arterial disease in other cases raises doubt about the alleged idiopathic nature of the myocardial or endocardial changes described.

Many, however, remain unclassified and no sharp differentiation is possible on either clinical or pathological grounds. They are usually men in the second to fifth decade presenting with symptoms of congestive heart failure often of short duration. The illness commonly runs a rapid downhill course and death may occur within a few months of the appearance of symptoms. At autopsy the heart is always enlarged, and may show varying degrees of endocardial and/or myocardial involvement, ranging from minor degenerative changes in the deeper layers of the myocardium (Reisenger and Blumenthal, 1941) to a picture of diffuse endocardial fibrosis, mural thrombus formation with multiple infarction in the viscera, and extensive fibrosis throughout the myocardium easily visible macroscopically (Smith and Furth, 1943; Ware and Chapman, 1947). All intervening grades of endocardial thickening and interstitial fibrosis and scarring may be seen. According to Fowler (1947), there is a progressive fibrosis of the heart from within outwards. A tendency for the subendocardial zone to be most affected is frequently noted, the left ventricle usually being involved.

In many respects, the morphological appearances resemble those of congenital fibro-elastosis, and on the few occasions when special staining methods have been used, a rich content of elastic fibres has been demonstrated in the thickened endocardium (Comeau, 1937; Elster *et al.*, 1955). In their 12 adult cases of chronic heart disease of obscure ætiology, aged 16 and upwards, Thomas *et al.* (1954) demonstrated abnormal degrees of endocardial fibro-elastosis and reached the conclusion that the lesion was congenital and of essentially the same nature as the infantile form. It is doubtful whether this conclusion is applicable to all adolescent and adult cases of idiopathic heart disease of the type just reviewed, but it certainly deserves serious consideration in the present case. The finding of extensive interstitial fibrosis does not appear to invalidate this opinion, and has already been reported in children with fibro-elastosis, e.g. in Thomas *et al.*, Case 7, where it was originally regarded as the essential lesion. The natural evolution of fibro-elastosis of the endocardium over a period of years in a surviving child cannot be defined until a thorough examination of many more hearts has been made, paying particular attention to the content and distribution of elastic tissue and concomitant interstitial fibrosis. The fibrosis may well be a sequel to the hypertrophy, for as pointed out by Roberts and Wearn (1941), increased muscle mass in cardiac hypertrophy may exceed the functional capacity of the capillaries thus impairing its metabolism. It is also possible that the myocardial changes observed in fibro-elastosis may be initiated by obliteration of the Thebesian vessels owing to the elastic thickening of the endocardium, as suggested by Gross (1941) and Halliday (1954).

The electrocardiogram in this case, showing the pattern of extensive transmural infarction, is of special interest and importance in view of the absence of coronary artery disease. Though conduction defects, arrhythmias, and ST–T wave changes are common in fibro-elastosis, we have been unable to find any other case of this disease or of heart disease of unknown ætiology in which cardiographic changes of the present type are reported or illustrated. For this reason the possibility of fibro-elastosis was not considered during life when the problem of ætiology arose. It is stressed now, not as a common or likely cause of an infarct pattern, but as a diagnosis that should be considered when this pattern is obtained from a young patient. While the cardiogram was characteristic of an infarction, the exact date of the onset of the lesion could not be determined. The first record suggested that it was of some weeks' standing, and in the chest leads the changing T waves during his first admission, compatible with healing myocardial damage, suggested that an active process was then taking place in the myocardium. Its exact nature, however, is obscure. Evidently in the process of establishing the sequence of the pathological changes in fibro-elastosis of the endocardium in surviving children and adolescents, it will be necessary to correlate them more and more precisely with the corresponding electrocardiograms.

Summary

A small group of reported cases has been abstracted to provide evidence that some patients with congenital endocardial fibro-elastosis may survive beyond infancy. The case is described of a youth, aged 15, who died in congestive heart failure. Post mortem, the heart was enlarged and showed well-marked endocardial fibro-elastosis, with mural thrombus formation and myocardial fibrosis.

The pathogenesis of the case is discussed in relation to congenital fibro-elastosis and to idiopathic heart disease in adults. The electrocardiograms were of unusual interest in showing the pattern commonly associated with extensive transmural myocardial infarction.

We are grateful to Professor I. G. W. Hill and Dr. R. J. Duthie for permission to publish the case, and to Professor J. S. Young and Professor Hill for much valuable help and advice. We wish to thank Mr. N. Mowat and Mr. F. M. Duncan, A.R.P.S., for skilled assistance and also the secretarial staff of our respective departments.

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ENDOCARDIAL FIBROELASTOSIS WITH GENERALIZED LYMPHADENOPATHY, ŒDEMA, AND RASH

BY

N. M. GIBBS, J. C. HAWORTH, AND JOHN RENDLE-SHORT

From the Department of Child Health, The University of Sheffield, and The Children's Hospital, Sheffield

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Endocardial fibroelastosis of the heart has attracted much attention in recent years and published case reports have been fully reviewed by Blumberg and Lyon (1952), Gowing (1953), and Dennis *et al.* (1953). A further review would seem unjustified, but we wish to report two cases of endocardial fibroelastosis associated with unusual clinical and pathological features.

Case Reports

Case 1. This boy was perfectly well until the age of eight and a half months when he developed a running nose with intermittent pyrexia and cough and his cervical lymph nodes were noticed to be enlarged. At the age of ten months his mother observed that he had a swelling in the left groin and that his feet and face were swollen. His urine was found to contain albumin. He was admitted to the Montagu Hospital, Mexborough, under the care of Dr. C. C. Harvey and at eleven months was transferred to the Sheffield Children's Hospital. On admission he was a pale, ill-looking child weighing 10·6 kg. with pitting œdema over his legs and back. He had a generalized enlargement of his lymph nodes, one in the left groin being especially prominent. His liver and spleen were both easily palpable but no other abnormal physical signs were detected. His heart at that time was thought to be normal. His blood pressure was 95/55.

Investigations. Urine: albumin 300 mg. per 100 ml., with an occasional granular cast but no red blood corpuscles. Hæmoglobin: 10·8 g. per 100 ml. W.B.C.: 3500 per c.mm. with a normal differential count. Bone marrow: hypercellular marrow with an increase in megakaryocytes including some abnormal forms: an abnormal marrow showing non-specific changes.

Blood cholesterol: 238 mg. per 100 ml. Blood urea: 28 mg. per 100 ml. Serum albumin: 2·4 g. per 100 ml. Serum globulin: 1·9 g. per 100 ml. Electrophoresis of the serum showed a decreased albumin and an increase of alpha 2 globulin; beta and gamma globulin were present in normal amounts. A four-day fat balance was normal.

A radiograph of the chest showed no abnormality. The Wassermann reaction was negative on mother and child. A posterior occipital node biopsy was performed. The findings will be discussed in the report of the pathological specimens.

Progress and Treatment. The child's condition grew gradually worse during the next six weeks. He developed small pleural effusions which were aspirated, the fluid containing 1000 mg. of protein per 100 ml., with a specific gravity of 1015. His urine never contained more than 12 R.B.C.'s per high-power field, but the albumin content rose to 900 mg. per 100 ml. At this stage he was a grossly œdematous child who preferred to sit upright in bed. As it was thought that he probably had the nephrotic syndrome, cortisone was given by mouth for seven days, but no diuresis occurred when the drug was withdrawn. Indeed, his œdema and dyspnœa grew worse and his pleural effusions were again aspirated, a total of 205 ml. of fluid being removed. Mersalyl $\frac{1}{2}$ ml. was

given intramuscularly and this produced a diuresis, although the œdema did not entirely disappear. Because of the satisfactory response to the drug, mersalyl 1 ml. was continued every other day, but the child became increasingly dyspnœic. Ten days before his death at the age of 13 months an apical systolic murmur was heard for the first time.

Necropsy Findings. The body was that of a male child weighing 8·8 kg. with generalized pitting œdema of the subcutaneous tissues. The œdema was most marked in the tissues of the face. There were large pleural effusions of 120 ml. on each side. The pericardium and pericardial cavity were normal. No ascites was present.

Cardiovascular System. The heart weighed 65 g. (normal 45 g.) and showed hypertrophy of the muscle of all chambers (left ventricle 9·0 mm., right ventricle 4·0 mm.). The endocardium was opaque with a pearly white colour. It was thickened throughout, that in the atria measuring 1·0 mm. and the ventricles 2·0 mm. The atrial walls showed no tendency to collapse after evacuation of blood clot, owing to the rigidity of the endocardium: thus the orifices of the venæ cavæ, auricular appendices, coronary sinus, and pulmonary veins remained widely patent. The mitral valve cusps were thickened and the valve orifice was converted into a rigid contracted opening. The remaining valves showed no abnormality. The coronary arteries were normal in appearance and distribution.

Other Organs. There was generalized enlargement of the lymph nodes, the mediastinal nodes showing the most conspicuous changes. On section the surfaces had a cystic appearance and exuded clear watery fluid. Both lungs were partially collapsed, congested, and œdematous. The liver weighed 317 g. (normal 304 g.). It was pale in colour. There was some enlargement of the spleen which weighed 38 g. (normal 26 g.). The kidneys (right 45 g., left 51 g., normal 35 g.) were enlarged, pale, and œdematous. There was no evidence of subcapsular or parenchymal scarring: the renal pattern was normal.

The histological findings will be discussed with those of Case 2.

Case 2. A previously healthy boy of four months was admitted to hospital with a left-sided otitis media and mastoiditis. A few râles were heard in his chest. He responded quickly to treatment with penicillin and was discharged home after four days. Ten days later his cough became worse, he went off his feeds and was noted to be generally unwell. After a further two weeks he was readmitted to hospital looking ill and weighing 9·1 kg. He was afebrile but was in some respiratory distress and bronchial breathing was audible at the left lung base. There was a large, tender, submandibular lymph node on the left side, and an urticarial rash on the trunk. An X-ray of the chest showed collapse of the left lower lobe. He was treated with intramuscular penicillin, 250,000 units six-hourly. The signs in the chest cleared in ten days and the submandibular node subsided. His urine contained albumin 1600 mg. per 100 ml., with an occasional pus cell and red blood cell.

He was seen as an outpatient about three weeks later when bronchial breathing was again heard at the left lung base and there were signs of generalized bronchitis. A further chest X-ray showed that the collapse of the left lower lobe persisted.

This child's third admission was at the age of seven months when there was increasing respiratory difficulty. Examination revealed a pale, ill baby who had some puffiness of the face but no detectable œdema elsewhere. There was a fine petechial rash on the neck, and brownish markings on the trunk looked like fading petechiæ. The signs in the chest were unchanged and he had a left suppurative otitis media. No abnormality was detected in the cardiovascular system. The urine contained 600 mg. per 100 ml. of albumin, but no increase in cells and no casts. A tentative diagnosis of nephrotic syndrome was made. He was given penicillin without much improvement and later aureomycin was substituted for the penicillin.

Investigations. Hæmoglobin: 10·4 g. per 100 ml. W.B.C.: 8000 per c.mm. with normal differential count. Platelets: 401,000 per c.mm. Serum proteins: albumin 2·5 g. per 100 ml., globulin 1·7 g. per 100 ml. Electrophoresis: increased alpha 2 globulin and decreased beta globulin. Serum cholesterol: 224 and 179 mg. per 100 ml. Blood urea: 25 mg. per 100 ml.

The patient's general condition remained unchanged and the cough and aural discharge per-

sisted. Two and a half weeks after admission he developed diarrhœa and vomiting and was reluctant to feed. The next day he was very ill and dehydrated. Intravenous fluids were given. Two days later, because of persisting diarrhœa, he was transferred to an isolation hospital.

He was readmitted from the isolation hospital after a further six weeks. His general condition was poor, and he had slight generalized œdema. He was cyanosed and in considerable respiratory distress. There were signs of a left-sided pleural effusion. He had a temperature of 99° F. Lymph nodes in the neck, axillæ, and groins were moderately enlarged and the spleen was easily palpable. There was a blotchy rash on the trunk which had a purpuric element (Fig. 1). The

FIG. 1.—Appearance of Case 2 during the fourth hospital admission.

heart was thought to be normal and there was no hypertension. Chest aspiration yielded 105 ml. of straw-coloured fluid which clotted readily and contained 850 leucocytes per c.mm., mainly lymphocytes. This fluid was sterile.

Other Investigations. Bone marrow biopsy, no gross abnormality. Kahn, and Wassermann reactions negative. Toxoplasma tests, negative. X-ray of chest: left-sided pleural effusion, collapse of the left lower lobe, partial collapse of the left upper lobe with herniation of the right lung across to the left; the heart shadow was partly obscured by fluid but was not thought to be enlarged.

Pleural aspiration was repeated on three occasions because of increasing respiratory difficulty, 140, 60, and 200 ml. of fluid being removed. Each time there was temporary improvement but the boy's general condition remained unchanged. The rash increased and involved the whole of the body. At this time adrenocorticotrophic hormone was given empirically, but seven days later the child's temperature rose and he died suddenly from respiratory failure. At the time of his death he was ten months old.

Necropsy Findings. The body was that of a well-nourished male child showing œdema of the subcutaneous tissues. There was a large left-sided pleural effusion with some thickening of the parietal pericardium, but no adhesions were present. There was no ascites.

Cardiovascular System. The heart weighed 62 g. (normal 39 g.) and showed hypertrophy and dilatation of all chambers. The wall of the left ventricle measured 11 mm., and that of the right ventricle 9 mm. There was endocardial thickening which was similar in distribution and

degree to that in Case 1. The endocardium of the atria was 1·0 mm. thick and that of the ventricles 2·0 mm. In addition the tricuspid valve cusps were thicker than normal and the mitral valve was reduced to a rigid contracted opening. The pulmonary and aortic valves appeared normal. The coronary arteries were also normal.

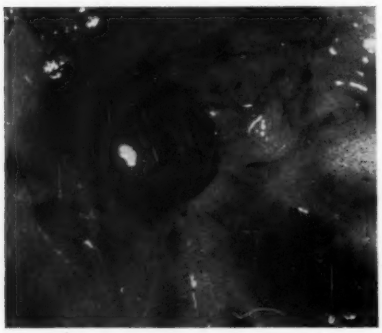

FIG. 2.—Internal mammary lymph cysts (Case 2).

Other Systems. The lymph nodes were distended with clear watery fluid. In particular the internal mammary lymph nodes were converted into thin-walled cysts (Fig. 2) and similar but less pronounced changes were present in the other lymph nodes. The lungs were collapsed, œdematous, and congested. The liver (448 g., normal 274 g.) and the spleen (30 g., normal 22 g.) were enlarged and firm. The kidneys (right 81 g., left 79 g., normal 32 g.) were large and pale and showed no subcapsular or parenchymal scarring.

Histology. The histological appearances of the heart, lungs, lymph nodes, and kidneys were similar in each case. In the *heart* the endocardium of the atria and ventricles consisted of thick fibroelastic tissue, which showed some variation in structure: that of the atria was composed of collagen with regularly spaced nuclei and contained large numbers of delicately undulating elastic fibres (Fig. 3), whereas the endocardium of the ventricles consisted of almost acellular hyaline collagen and fragmented elastic fibres. The mitral valves in both cases and the tricuspid valve in Case 2 showed the typical changes that have been described in fibroelastosis (Craig, 1949). The ventricular muscle fibres showed hypertrophy. All lobes of the lungs of both cases showed œdema with alveolar collapse and congestion. Numerous hæmosiderin-containing macrophages were present within the alveoli.

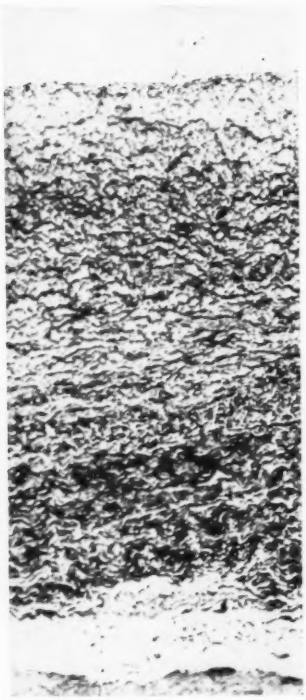

FIG. 3.—Endocardium of left auricle, ×75 (Case 1). Weigert's resorsin fuchsin and Van Gieson.

Lymph nodes (including biopsy of posterior occipital lymph nodes in Case 1). Lymph nodes examined from each of the main groups showed great dilatation of the lymphatic sinuses which were filled with acellular lymph (Fig. 4 and 5). The lymph follicles contained plasma cells and mononuclear macrophages, in addition to lymphocytes. The lymph node capsules were occasionally thickened. Those of the internal mammary lymph nodes of Case 2 revealed the most conspicuous changes and were surrounded by cellular connective tissue. There was general dilatation of the lymphatics associated with interstitial œdema. The tissues adjacent to the lymphatic channels contained a few plasma cells and lymphocytes.

In both cases conspicuous interstitial œdema was seen in the *kidneys* with occasional foci of plasma cells and lymphocytes. The glomerular tufts and tubules were normal. In each case the lymphatics in the portal areas of the *liver* were distended with lymph (Fig. 6) and some intracellular fat droplets were demonstrated at the periphery of the liver lobules. The typical appearances of chronic venous congestion were not present.

The following additional histological lesions were found in

FIG. 4.—Biopsy of posterior occipital lymph node. Hæmatoxylin and eosin. ×8. Case 1.

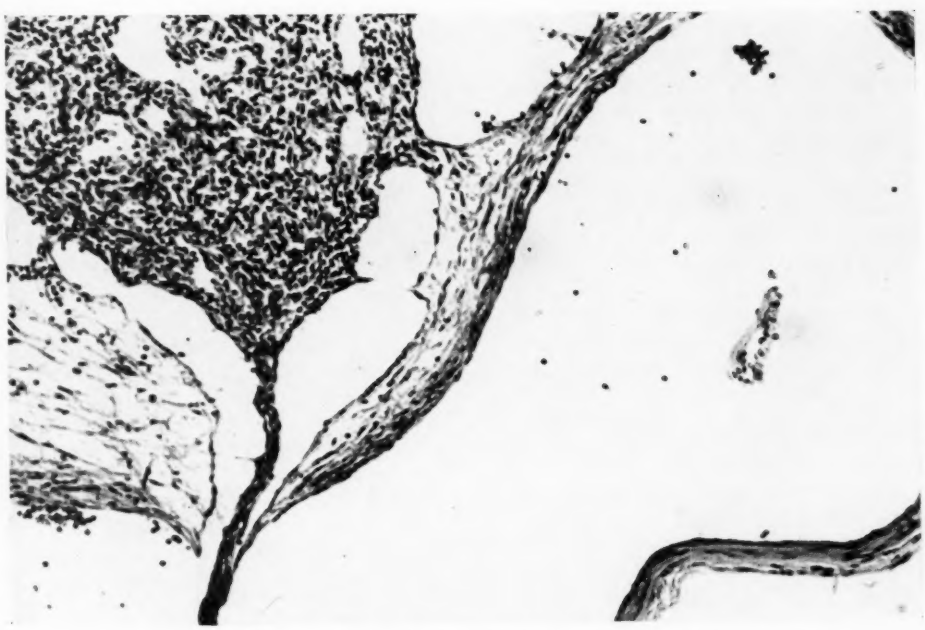

FIG. 5.—Lymph sinuses from node shown in Fig. 4. Hæmatoxylin and eosin. ×100.

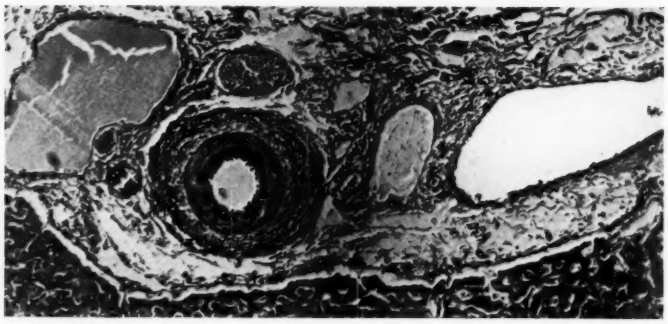

FIG. 6.—Portal lymphatics in liver. Verhœff hæmatoxylin and Van Geison. ×55. Case 2.

Case 2: the *pericardium* was composed of hyaline collagen, which contained no elastic fibres and was relatively avascular. The dermis of the *skin* showed changes similar to those seen in the interstitial tissues elsewhere, namely vascular dilatation and distended lymphatics. Lymphocytes and plasma cells were present. The epidermis was normal.

DISCUSSION

The clinical features of the two cases were remarkably similar. They were boys of about the same age, being 13 and 10 months respectively when they died. They were both apparently quite healthy for the first few months of life and then presented with respiratory disease, œdema, and generalized lymphadenopathy. The urine of both children contained a large amount of albumin but very few red blood cells or casts were seen. Serum proteins were low in each case, with a reduction of the albumin fraction, and both children were at one time thought to be suffering from the nephrotic syndrome. The electrophoretic pattern, however, although similar in the two cases, was not typical of the nephrotic syndrome and the blood cholesterol was not appreciably raised. The course of the disease was slowly progressive, with increasing œdema and pleural effusions which required aspiration. Cortisone in Case 1 and adrenocorticotrophic hormone in Case 2 did not affect the course of the disease, and in fact these drugs may have precipitated the fatal issue. In neither case was cardiac failure seriously considered, although in Case 1 mersalyl caused some improvement and ten days before death an apical systolic murmur was heard. In neither child was the heart enlarged clinically or radiologically and retrospective examination of the chest radiographs does not reveal any abnormality of the cardiac silhouettes.

A remarkable feature in Case 2 was the rash. During the second hospital admission it was urticarial, but petechiæ were noted later; the platelet count, however, was normal. Large dark red blotches appeared terminally over the trunk and extremities.

In a survey of previously published records we have not been able to find reports of cases of endocardial fibroelastosis with clinical findings such as these. The clinical features of the condition have recently been reviewed by Dennis *et al.* (1953). Neither œdema, generalized lymphadenopathy, albuminuria, nor rash were mentioned in their review of the signs and symptoms of the disease. Radiographic enlargement of the heart was found in 85 per cent of cases in which radiology was performed.

Gowing (1953) described a case of fibroelastosis with generalized lymphadenopathy and Prior and Wyatt (1950) mentioned cases with mesenteric lymphadenopathy associated with ascites, but no additional details were given. In our cases the generalized lymphadenopathy was caused by extreme dilatation of the lymph node sinuses with lymph. The resulting lymph cysts were most

conspicuous in the internal mammary nodes in Case 2, where the lymph node capsules were thickened and surrounded by cellular connective tissue.

There are two possible reasons for the production of these lymph cysts: (1) increase in the volume of lymph flow or (2) lymphatic obstruction. An increase in the volume of lymph flow occurs when there is œdema of the interstitial tissues, but no previous account of generalized lymphadenopathy with the formation of lymph cysts has been found. Increased lymph flow might be expected to occur in congestive cardiac failure, and enlargement of the hilar lymph nodes has been recorded in this condition by Bouvrain and Bescol-Liversac (1950). Pathological evidence of systemic venous congestion in our cases was, however, lacking and in any case there is no reason why increased lymph flow per se should result in cyst formation. It would seem, therefore, that the second possibility, namely lymphatic obstruction, was the factor responsible for the formation of the lymph cysts. It was not possible to determine histologically whether the obstruction was in the lymph channels or in the nodes themselves.

In both our cases albuminuria was gross and continuous. Albuminuria of moderate degree is common in congestive cardiac failure and is attributed to changes in the permeability of the glomerular capillary loops produced by engorgement of the renal venous radicles, but as has been stated, no macroscopic or microscopic appearances of chronic venous congestion were found. In addition, no nephron lesions were identified, the enlargement and pallor of the kidneys being produced by interstitial œdema. Dilated lymphatic channels were prominent and it is possible that the albuminuria was related to the deficient disposal of the interstitial fluid in the kidneys.

The fibroelastic process in our cases was unusually widespread and extensive. All chambers of the two hearts were involved, including the right atria, though the right side of the heart in this condition is generally much less often affected than the left. In 149 cases reviewed by Dennis *et al.* (1953) the process was limited to the left side in 82 per cent and only two reports of involvement of the right atrium has been found by us (Hill and Reilly, 1951; Collier and Rosahn, 1951). Both our cases showed thickening of the mitral valve and in Case 2 the tricuspid valve was also affected. Tricuspid stenosis was present in only 10 of 149 cases reviewed by Dennis *et al.*

Both our cases presumably died from cardiac failure, although the fact that chronic venous congestion was not found in the organs at necropsy would suggest that the failure was acute, and possibly only the terminal event in a generalized morbid process in which the heart, among other tissues, was involved. Certainly Case 2, right up to the end of his life, seemed to be suffering from an acute disease as evidenced by an intermittent temperature and a rash, which frequently changed in appearance.

The cause of cardiac failure in fibroelastosis remains uncertain. Gross (1941) and Weinberg and Himelfarb (1943) suggested that failure is the result of ischæmia of the subendocardial muscle produced by vascular stasis, this in turn resulting from obstruction of the Thebesian veins by the thickened endocardium. However, the endocardium in our cases was so much thickened and so rigid that it could easily be imagined that it interfered mechanically with the action of the heart and this, together with the valve lesions, precipitated failure. This supports one of the hypotheses of Prior and Wyatt (1950) and, indeed, it seems probable that the cardiac failure in endocardial fibroelastosis is similar in mechanism to that in constrictive pericarditis, for in each disease the action of the heart is impeded by a dense investment with connective tissue. It is interesting to speculate whether the unusual thickening of the endocardium in our cases prevented the chambers dilating and thus accounted for no cardiac enlargement being detected clinically.

The ætiology of endocardial fibroelastosis remains unknown. Kempton and Glynn (1955) have recently discussed the various suggestions made. Our two cases were characterized by an unusually diffuse involvement of the heart together with evidence of lymphatic obstruction and in addition, a generalized skin rash in Case 2. It seems reasonable to postulate that the endocardial fibroelastosis, lymphatic obstruction, albuminuria, and skin rash were all manifestations of a generalized disease, the origin of which remains obscure.

Summary

Two cases of endocardial fibroelastosis are presented. The clinical features of the cases showed a close similarity. After being healthy for the first few months of life, both boys developed respiratory infections, gross œdema, generalized lymphadenopathy, albuminuria, and low serum albumin. In addition, one child had a rash.

The pathological findings in the two cases were very similar. There was extensive endocardial fibroelastosis involving all four chambers of the heart and cystic enlargement of the lymph nodes.

These cases raise the possibility that the cardiac lesions in endocardial fibroelastosis are merely local manifestations of a generalized disease.

We should like to thank Dr. C. C. Harvey who supplied us with the early history of Case 1, Dr. H. G. Koster who performed the necropsy in Case 2, Dr. J. L. Emery for his help with the pathological findings, and the Photographic Department of the Sheffield United Hospitals for the illustrations. Case 1 was admitted under Professor R. S. Illingworth and Case 2 under Dr. T. Colver, to both of whom our thanks are due for permission to publish and also for helpful criticism.

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THE AORTA AND PULMONARY ARTERIES IN FALLOT'S TETRALOGY

BY

J. NORMAN PATTINSON* AND RICHARD W. EMANUEL

From the Departments of Radiodiagnosis and Cardiology, Middlesex Hospital

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Until the last decade our knowledge of the anatomy in Fallot's tetralogy had been derived from clinical observations, radiology, and post-mortem specimens. The advent of cardiac catheterization and particularly angiocardiography gave additional methods of studying this condition during life. Our observations are based on angiocardiograms that we carried out in 60 cases of Fallot's tetralogy. In addition to the usual findings which are now well recognized (Steinberg and Dotter, 1951; Lowe, 1953; and Hilario *et al.*, 1954), we have been able to add certain observations on the aorta and its branches and also on the right and left pulmonary arteries (R.P.A. and L.P.A.) which we record here.

In all cases, angiocardiograms were taken in the antero-posterior (A.P.) position. In some instances the right anterior oblique position (R.A.O.) was used when a second examination was required to demonstrate the site of the stenosis. We found the left anterior oblique position (L.A.O.) to be the optimum view in assessing the degree of aortic override. All examinations were performed with the patient supine on a single plane film changer providing films at approximately 0·8 second intervals at an anode-film distance of 48 inches.

The Aorta in Fallot's Tetralogy

The overriding aorta is of course one of the diagnostic features of the tetralogy. On angiocardiography this is shown by early opacification, as the aorta fills simultaneously with the pulmonary trunk from the right ventricle.

In Fallot's tetralogy the ascending aorta is always enlarged particularly in adults. A good example of this is shown in Fig. 1 from a woman, aged 52, who had been under observation for 20 years (Bedford, 1929 and 1956). In cases of pulmonary atresia a giant aorta may be seen (pseudo truncus arteriosus), the so-called truncus aorticus of French authors. Brinton and Campbell (1953) found the diameter of the aorta averaged 17·1 mm. compared with 10·4 mm. for the pulmonary trunk in 25 specimens at necropsy, whereas the two vessels are approximately equal in diameter in the normal.

On the plain X-ray the aortic knuckle is always visible in Fallot's tetralogy unless obscured by a left superior vena cava. The large comma-shaped ascending aorta usually imparts an increased convexity to that part of the right pedicular contour, formed by the superior vena cava. This is in contrast to pulmonary valvular stenosis with a normal aortic root, where the aortic knuckle is often insignificant and obscured by a large left pulmonary artery and that part of the right pedicular contour formed by the superior vena cava and adjacent aorta is straight (Bedford, 1955).

The abnormal size and shape of the aorta and aortic arch in Fallot's tetralogy can be best studied from angiocardiograms. In the A.P. position the ascending aorta is large and forms an unusually prominent arc to the right as already described and in many cases, owing to the dextroposition of the aortic root and the shape of the ascending aorta, the ascending and descending

* Duchess of Bedford Research Fellow.

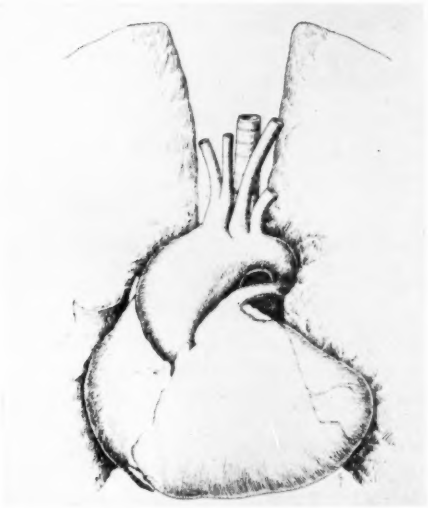

FIG. 1.—Fallot's tetralogy. Woman, aged 52 years. Specimen drawn *in situ*, showing unusually large ascending aorta narrowing abruptly at the isthmus.

limbs of the arch are more widely separated (Fig. 2A and C). These observations apply only to cases with a left-sided aortic arch. The widening of the aortic arch and increased curvature of the ascending limb can be seen best in the L.A.O. position (Fig. 2B and D). Another characteristic feature of the aortic arch in Fallot's tetralogy is the sudden narrowing of the vessel that occurs immediately distal to the origin of the left subclavian artery. We found one exception to this where the aortic arch suddenly narrowed 5 cm. distal to the origin of the left subclavian artery.

In order to demonstrate these points we measured the width of the aortic shadow when filled with contrast medium at the upper level of the twelfth dorsal vertebra, at the arch just distal to the origin of the left subclavian artery and 2 cm. above the valves. The ratio of these measurements were compared. The actual aortic sizes could not be used owing to the wide range of ages and differing body builds in a relatively small number of observations. These findings were compared with similar measurements obtained from a small series of cases in which angiocardiograms had been done for pulmonary lesions, the heart and aorta being normal. In normal cases the ratio of the aortic diameters at the three sites mentioned above (descending aorta, arch of aorta, and root of aorta) was 1 : 1·3 : 1·7 compared with 1 : 1·7 : 2·4 in Fallot's tetralogy.

The degree of aortic override in Fallot's tetralogy is difficult to assess from angiocardiograms. A fair estimate can be made, however, from the relation of the aortic root to the interventricular septum, which is best demonstrated in the L.A.O. position. It appears that the more anterior the aortic root in this view, the greater the degree of override. We could find little if any correlation between the diameter of the ascending aorta and the amount of override either in our cases or from a study of the necropsy figures published by Donzelot *et al.* (1952). This may be due to the varying calibre of the aorta with age.

A separate series of 13 necropsy specimens from cases of Fallot's tetralogy have also been examined and the observations concerning the size and shape of the aorta were confirmed. Unfortunately only one of these cases was studied angiocardiographically before death.

There was a right-sided aortic arch in 12 cases (20%) of our series. In all these patients the

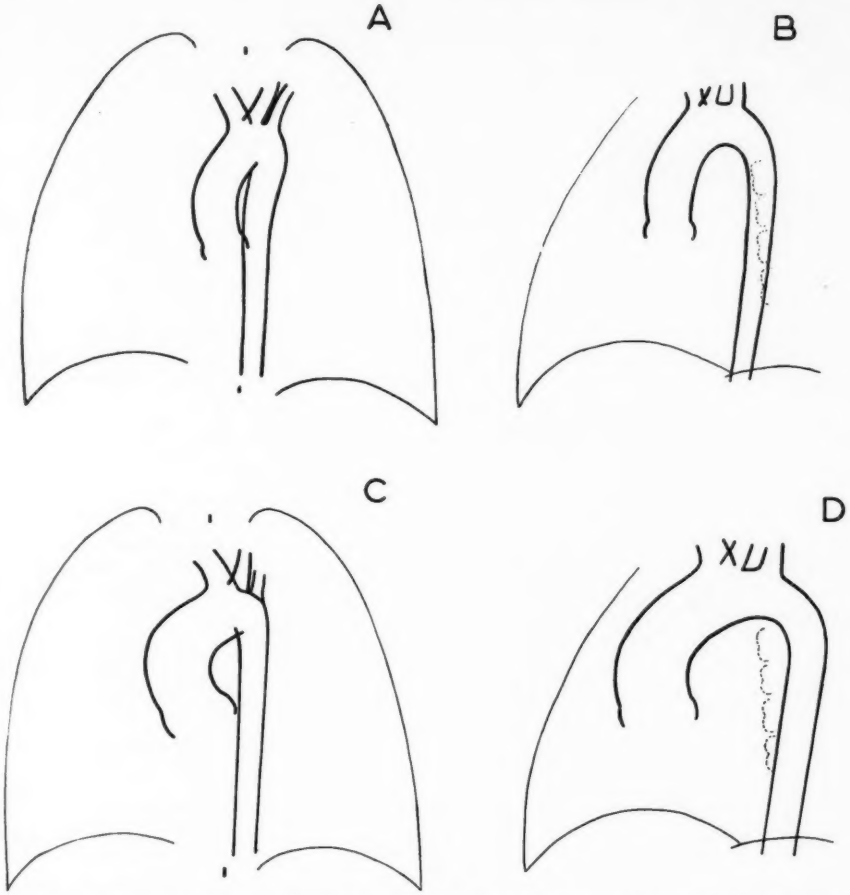

FIG. 2.—Diagrams of the normal aorta and the aorta in Fallot's tetralogy. (A) Normal aorta (A.P.). (B) Normal aorta (L.A.O.). (C) Aorta in Fallot's tetralogy (A.P.). (D) Aorta in Fallot's tetralogy (L.A.O.).

upper part of the descending aorta lay on the right side and crossed to the left of the midline in the lower third of the thorax. In such cases the right-sided aortic arch and its branches commonly form a mirror image of the normal, the first branch of the arch being a left innominate artery. In one of our cases, however, the left common carotid artery was the first branch while the left subclavian artery originated as the fourth and last branch from the arch and ran a retro-œsophageal course.

We obtained good visualization of the aortic branches in 43 out of 48 cases with a left-sided aortic arch. An anomalous retro-œsophageal right subclavian artery was present in 6 (14%). Four of these have been previously described in greater detail by one of us (Pattinson, 1953). This incidence is much higher than that in the general population quoted at 0·6 per cent (Holzapfel, 1899) to 0·8 per cent (Cairney, 1925). In our experience there is no unusual frequency of an anomalous right subclavian artery in other forms of congenital heart disease.

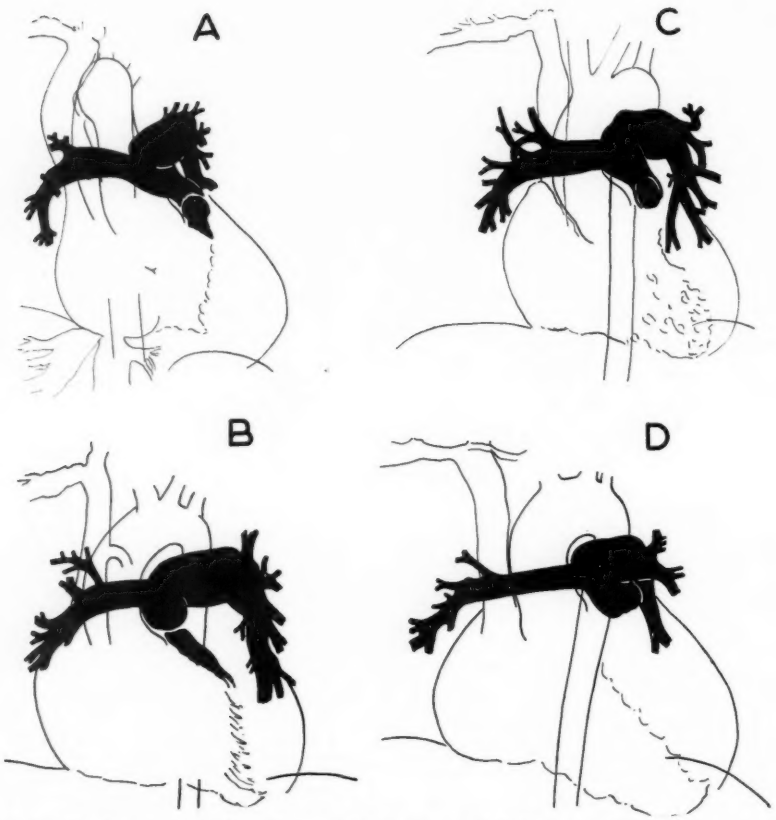

FIG. 3.—Tracings from angiocardiograms in four cases of Fallot's tetralogy in which the left pulmonary artery is larger than the right. (A) Woman, aged 50 years. (B) Boy, aged 6 years. (C) Boy, aged 5 years. (D) Girl, aged 9 years.

THE PULMONARY ARTERIES IN FALLOT'S TETRALOGY

The site of the pulmonary stenosis in Fallot's tetralogy can be determined in the majority of cases, particularly if angiocardiograms are taken in two views (A.P. and R.A.O.). If, however, the films are taken at intervals of 0·8–1·0 sec., great care must be taken in diagnosing abnormalities of the infundibulum as the shape of this muscular chamber varies greatly with the various phases of the cardiac cycle.

The pulmonary trunk is frequently small in Fallot's tetralogy partly accounting for the concave or straight pulmonary artery segment seen in the plain X-ray. In one-third of our cases we found considerable difference in the diameter of the two pulmonary arteries, when measured 1 cm. from the bifurcation of the pulmonary trunk. This difference amounted to 0·5 cm. or more in 19 out of 60 cases and in 17 instances it was the left that was larger than the right. Fig. 3 shows four typical examples. This was an unexpected finding as in the normal the right is a little larger than the left (Schafer and Thane, 1899; Brash, 1951; and Johnston and Whillis, 1947). There is probably an embryological explanation for this finding and therein may lie further support for Bremer's

view, that the adult right and left pulmonary arteries arise from different embryological structures (Bremer, 1909; Emanuel and Pattinson, 1956).

The site of the stenosis was visualized in 15 of the 19 cases where there was unequal division of the pulmonary trunk. Both the pulmonary valve and infundibulum were abnormal in 13 cases, while in the remaining 2 the infundibulum alone appeared stenosed. Where the size of the R.P.A. and L.P.A. were equal the site of the stenosis was visualized in 33 of the 41 cases. The pulmonary valve and infundibulum were abnormal in 14, the valve alone was involved in 2 cases, while in the remaining 17, the stenosis appeared to be confined to the infundibulum. Thus pulmonary valvular stenosis was more frequent in the cases where there was unequal division of the pulmonary trunk. It must be remembered, however, that with the technique used an infundibular stenosis may mask a co-existent pulmonary valvular stenosis.

In only one case where there was unequal division of the pulmonary trunk did we have the opportunity of confirming our observations at necropsy; this was in a male, aged 19, where the L.P.A. was larger than the R.P.A.

The unequal size of the pulmonary arteries was never sufficient to cause any difference in opacification of the periphery of the lung fields.

A rare anomaly in Fallot's tetralogy is the absence of the left pulmonary artery. We have recorded 2 cases and reviewed a further 18 (Emanuel and Pattinson, 1956).

Summary

In Fallot's tetralogy the ascending aorta is enlarged. It narrows rapidly at a point immediately distal to the origin of the left subclavian artery. Owing to the dextroposition of the aortic root and shape of the ascending aorta the ascending and descending limbs of the arch are more widely separated than in the normal.

In all our cases associated with a right-sided aortic arch the descending aorta crossed to the left of the midline in the lower third of the thorax.

In Fallot's tetralogy an anomalous retro-œsophageal right subclavian artery occurred in 14 per cent of cases, compared with a frequency of about 0·7 per cent in the population as a whole.

In a third of our cases of Fallot's tetralogy there was unequal division of the pulmonary trunk (19 out of 60 cases) and in the majority (17 instances) the left pulmonary artery was the larger branch. Unequal size of the pulmonary arteries did not appear to affect the lung filling.

We wish to thank Doctors Evan Bedford and Walter Somerville for their help with this paper.

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DILATATION OF THE AORTA DUE TO GRANULOMATOUS (GIANT-CELL) AORTITIS

BY

J. V. O. REID

From the Pathological Laboratory, Radcliffe Infirmary, Oxford

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Syphilis is generally considered to be the most frequent cause of gross aortic dilatation, but there are a number of other causes of this condition, and this paper draws attention to the occurrence of aortic dilatation in association with granulomatous (giant-cell) arteritis.

In syphilis the dilatation occurs in the ascending part and arch of the aorta. The aorta is dilated proximal and distal to a coarctation. In the presence of aortic valvular disease the ascending part may widen. In hypertension widening of the ascending part and arch may occur, though never to any great extent. Cystic medial necrosis with or without dissection may produce dilatation, particularly of the ascending aorta, and sometimes this becomes aneurysmal (Erdheim, 1929). Arteriosclerotic aneurysmal dilatation of these parts has been described. Ruffin *et al.* (1941) have reported three cases of a condition they call senile ectasia of the aorta, in which the ascending aorta is dilated in the absence of atherosclerosis.

Granulomatous aortitis, as a further cause of aortic dilatation, is less commonly recognized, although it has been shown repeatedly that "giant-cell" temporal arteritis is a generalized disease of large arteries (Cooke *et al.*, 1946; Harrison, 1947). The particular liability of the aorta is shown by the observation that in every reported case of cranial arteritis where the aorta has been adequately examined microscopically, characteristic changes have been found. These cases, together with those having aortitis without cranial arteritis, have been enumerated by Cardell and Hanley (1951). Their list does not mention Sproul's case (1942) as having aortitis. Further examples were summarized by Heptinstall *et al.* (1954). Cases that should now be added are those of Magarey (1950), Rywlin and Kuschner (1953), and possibly those of Harbitz (1926), Shennan (1934) (Case 3), and Weber (1950). In all, twenty-one instances excluding the three possible ones, have been reported in which the aorta has been examined microscopically, and in all there has been an aortitis. The temporal artery was not involved in every case.

Dilatation of the aorta due to this condition has been reported before (Sproul and Hawthorne, 1937; Cooke *et al.*, 1946; Weber, 1950). The aorta of Shennan's Case 3 (1934) had histological features suggestive of granulomatous aortitis; it was dilated in its ascending part. As regards other arteries, one of Gilmour's patients (1941) with granulomatous aortitis had an aneurysm of a subclavian artery. Dick and Freeman (1940) reported a case with a radiological appearance of innominate artery expansion, while Harrison *et al.* (1955) have described one with saccular aneurysms of large arteries.

In this paper four further examples of aortic dilatation due to giant-cell aortitis are reported.

Case Histories

Case 1. A farmer, aged 65, had had rheumatic fever and paratyphoid fever in childhood, and pleurisy at the age of 35. Early in 1954 he had muscular pains in the arms, legs, and shoulders. In May of that year he developed œdema, ascites, and attacks of cardiac asthma. He was said to be hypertensive. From this episode he recovered with rest in bed and digitalis. Severe occipital headaches occurred in August, 1955, seeming to be located in the scalp. Two days before admission on 1/10/55, he began to have loss of vision and ocular pain.

Examination. A well-looking intelligent man. Blood pressure 175/100. Cardiac apex beat at the nipple line. Presystolic gallop rhythm present. On retinoscopy slight bilateral blurring of disc margins; the left upper quadrants of both visual fields alone were preserved. He was tender over the right occipital

artery; the temporal pulses were absent, but these arteries were not tender. Moderate changes of rheumatoid arthritis were present in all joints of the limbs. E.S.R.: 135 mm. in one hour. X-ray of the skull showed no abnormality. Chest X-ray showed enlargement of the left ventricle with widening of the ascending aorta (Fig. 1). Rose's differential agglutination test: weak positive (differential titre 16). A lumbar puncture revealed normal pressure and cerebrospinal fluid.

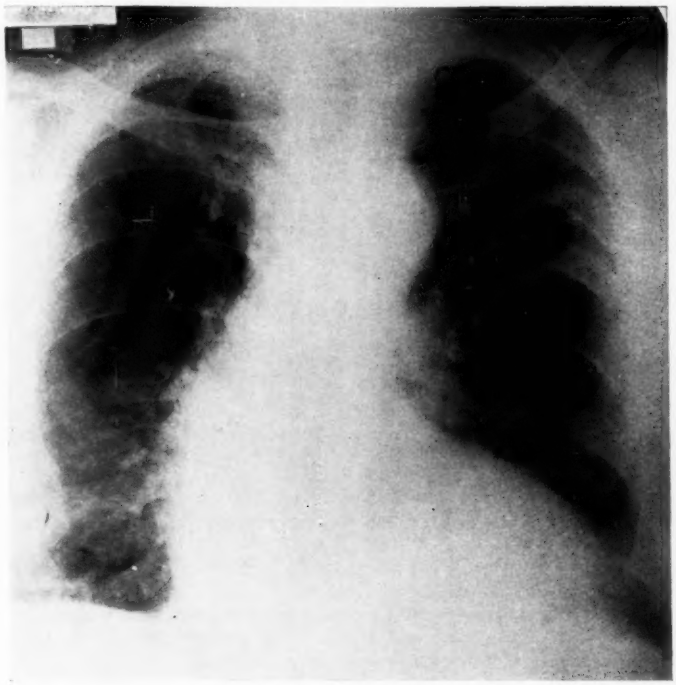

FIG. 1.—Case 1. X-ray, showing the dilatation of the ascending aorta, which was not as much in this case as in the others.

Progress. A diagnosis of cranial arteritis was made and he was treated with cortisone. All vision rapidly disappeared after admission. Two weeks after admission he complained of severe chest pain, and a pericardial friction rub became audible. An electrocardiogram showed left axis deviation, digitalis effect, and almost certain underlying ischæmic heart disease; there was no sign of cardiac infarction. His condition worsened, and he died three weeks after admission.

Post-mortem examination (P.M. 709/55). Rheumatoid arthritis of joints of hands and wrists, with mild changes in larger joints. *Cardiovascular system.* Hæmorrhagic pericarditis, the cavity containing 150 ml. of bloody fluid. Both ventricles were dilated and their walls somewhat hypertrophied. Mitral cusps and chordæ were thick and opaque, the valve admitting three fingers. Diffuse fibrosis of the myocardium was present and the coronary arteries were atheromatous. The aorta was dilated in its ascending part; no measurements were taken but the size was quite conspicuous; there was calcified atheroma of the abdominal part. No macroscopic abnormality was found in any of the larger or smaller arteries.

Microscopical findings. Granulomatous aortitis most severe in the apex of the arch and in the descending part in the thorax. Arteritis of the coronary, internal carotid, ciliary, ophthalmic, and femoral arteries. Hæmorrhagic pericarditis with very little inflammatory cell infiltrate. Fairly severe myocardial fibrosis, both diffuse and perivascular. The lesion in this patient was not as severe histologically, nor the dilatation of the aorta as great, as in the other cases.

Case 2. A farm labourer, aged 71, gave no significant past history. In April, 1946, he began to have occipital headaches, and in July of that year hæmaturia, for which he was referred for investigation.

Examination. A well-nourished man. Blood pressure 140/90. The temporal and brachial arteries were very tortuous. Wassermann and Kahn tests negative. An X-ray of the skull was normal. X-rays of the chest showed emphysematous lungs and calcification of aortic arch. E.S.R. 118 mm. in one hour. He was referred to Mr. J. Pennybacker, who considered the headaches to be due to cranial arteritis. By October, 1946, the headaches were considerably improved and soon disappeared. At this time he was admitted to hospital. Subsequent findings were absence of pulsation in the left leg at or below the knee, and in the right dorsalis pedis artery. The left plantar reflex was extensor, but there were no other neurological signs. E.S.R. 55 mm. in one hour. White cell count 9000/c.mm. Lumbar puncture: normal pressure and fluid; Wassermann reaction negative. Cystoscopy showed a papilloma of the bladder which was treated by repeated diathermy.

Progress. Hæmaturia continued and in June, 1947, at further cystoscopy the lesion appeared malignant. It finally caused acute retention of urine, and the patient died in January, 1948.

Post-mortem examination. (P.M. 28/48). A wasted old man. There was atrophic emphysema of the lungs. The carcinoma of the bladder had spread extensively in the pelvis, and the kidneys showed hydronephrosis and chronic pyelonephritis. *Cardiovascular system.* Right ventricle dilated. Valves normal. The *aorta* was dilated throughout its thoracic part, with intimal irregularity suggestive of syphilitic aortitis. Coronary arteries atheromatous.

Microscopical findings. The tumour was a transitional-cell carcinoma. Granulomatous aortitis was present with much atheroma.

Case 3. A widow, aged 70, had had acute rheumatism at the age of 12, and the heart was said to be affected ever since. During 1952 she began to have pain in her head, on the right side, and in the right ear. On 10/6/54 there was sudden onset of deadness in the left leg, for which she was admitted.

Examination. A thin old woman. Blood pressure 210/75. Auricular fibrillation. There were mitral systolic and diastolic murmurs. The left femoral pulse was absent and the left leg was cold and mottled. Mild rheumatoid arthritis in the hands. E.S.R. 11 mm. in one hour. White blood count 14,000/c.mm. Electrocardiogram: auricular fibrillation. An X-ray showed calcification of the aortic arch, and a cardiac configuration of mitral stenosis, but no hypoplasia of aorta; if anything there was slight dilatation.

Progress. The patient was treated for the incipient gangrene of the leg. Three weeks after admission she had a sudden right hemiplegia with aphasia, from which she did not recover.

Post-mortem examination (P.M. 413/54). The body of an old woman with swelling and discoloration of the left leg below the mid-thigh. *Cardiovascular system.* Dilatation of the left atrium and right ventricle. No antemortem thrombus in the atria or their appendages. Foramen ovale closed. The mitral valve had thick calcified cusps rolled down into the ventricle and admitting one finger only. The aortic cusps were normal and the valve supported a column of water. The myocardium of the left ventricle was diffusely fibrotic, and there was coronary atheroma. *Aorta.* Some calcification throughout, including the ascending part. This was conspicuously widened, quite out of keeping with an effect of hypertension and unexpected in view of the mitral stenosis. Thrombus in the abdominal aorta adherent to an atheromatous plaque. Both common iliac arteries and the left internal iliac were thrombosed. The common carotids, and the internal carotids as far as 4 cm. beyond the bulbs, were normal. Old wedge infarct of the spleen. Benign nephrosclerosis with two small infarcts in each kidney. The left middle cerebral artery was thrombosed and there was softening of a corresponding area of the brain.

Microscopical findings. Granulomatous aortitis (Fig. 2) and arteritis affecting the femoral and iliac arteries. The carotid arteries were not examined. The middle cerebral artery showed atheroma at a point distal to the thrombus; no sections were taken through the attached thrombus itself. The other findings confirmed the macroscopic appearances.

Case 4. A woman, aged 81, was said to have had indigestion and kidney trouble for years. Three days before death she had a hæmatemesis and this recurred on the day of admission. She died on being taken into the admission room.

Post-mortem examination (P.M. 1/55). The body of an obese old woman, with anæmia of all organs. There was a large chronic duodenal ulcer with a bleeding point in its base. The intestine was full of blood and there was much inhaled blood. The liver looked normal. The kidneys had finely granular surfaces without much scarring on the cut surfaces. *Cardiovascular system.* The pericardium was adherent by fairly easily broken fibrous adhesions. The right ventricle was dilated. The left ventricular myocardium

FIG. 2. Aorta of Case 3. A high-power view shows the cellular inflammatory infiltrate, in which four giant-cells lie along the site of the internal elastic lamina, and the media is almost entirely replaced. (×200).

FIG. 3.—Aorta of Case 4. There are two bands of inflammatory tissue, at the outer and inner parts of the media. The inner band replaces the internal elastic lamina, and the media between the bands is infarcted. (×100).

was scarred anteriorly. The valves and aortic ring were normal. The coronary arteries had normal ostia and mild general atheroma. *Aorta.* Much dilatation of the ascending aorta and arch, greater still in the upper part of the descending aorta, where it formed a fusiform aneurysmal expansion, but decreasing from there downwards. The intima was puckered in the ascending limb with star formation; there was extensive atheroma of the arch overlying similar scars. There was a large flat clot lying in the aneurysmal expansion of the arch beyond the origin of the three great vessels; its length was 10 cm.

Microscopical examination. Benign nephrosclerosis. The aorta showed a severe granulomatous aortitis in an active cellular stage (Fig. 3). Miliary granulomata not of classical sarcoid type in the lungs and liver. This case differs from the others in the presence of these granulomatous lesions.

DISCUSSION

In none of these cases was the aortic dilatation ascribable to the hypertension, where recorded, or to the amount of left ventricular hypertrophy revealed at necropsy examination.

In all of these four cases the histological picture was unlike that of syphilis and like that of previously described cases of granulomatous aortitis. A fifth case with an aneurysmal dilatation of the ascending aorta has not been included because of lack of supporting evidence, but in it also the histological picture of the aorta was quite unlike syphilitic aortitis. The microscopical appearances of the condition will be described in more detail elsewhere. In brief, the essential change is an inflammatory cell infiltration of the media, with some tendency to form into bands but not favouring any part of the media more than another (Fig. 2). The cells are plasma cells, lymphocytes, and larger mononuclear cells. Giant cells are usually present and may be numerous, but may on the other hand be very difficult to find. This applies to cases with known temporal arteritis as well

as to the cases without. The infiltration is usually diffuse, but may collect into foci with normal-looking media between them. There is destruction of the muscular and elastic elements of the media, particularly at the foci. These later scar and the inflammatory cells disappear. There is a tendency for bands of media to undergo an infarction-like process (Fig. 3). The mucoid change described in temporal arteritis is often present. Formation in the media of new capillaries is normally slight and is always much less in relation to the amount of inflammatory change than it is in syphilitic aortitis.

The intima is affected only by atheroma. The adventitia invariably shows some lymphocytic infiltration in the loose tissue or around vessels. It is sclerotic in older cases. Small arteries and arterioles in the adventitia show no endarteritis.

The difference from the syphilitic lesion lies in the presence of diffuse inflammation, its tendency to a band-like distribution, the paucity of new vessels, its exuberance in relation to other changes and in the absence of endarteritis of the vasæ or of characteristic microgummata. The fact that the aorta is affected in granulomatous aortitis may be recognized in life in a patient with temporal arteritis, not only by the dilatation of the aorta but also by its calcification. Where there is calcification without dilatation it is, of course, impossible to be absolutely sure; but the likelihood that an aortitis is responsible must be very great because of the high incidence, described above, in cases where the aorta has been examined microscopically.

Most cases of granulomatous arteritis are recognized because they have temporal or ophthalmic arteritis. Some (Rywlin and Kuschner, 1953; Finlayson and Robinson, 1955, Case 3) suffer gangrene of a leg due to thrombosis of its arteries. Histological examination of the artery in the amputated limb may then reveal the diagnosis. Thrombosis of the common or internal carotid arteries is a further feature in published cases (Gilmour, 1941; Harbitz, 1926; Ritama, 1951; McMillan, 1950), and at necropsy carotid involvement has nearly the same high incidence as the aortitis. For this reason granulomatous arteritis should be thought of in patients with this presentation. Here again, X-ray examination of the aorta may help, and a high E.S.R. corroborate.

Summary

Case reports of four patients have been given together with records of the findings at necropsy. Aortic dilatation due to granulomatous (giant-cell) aortitis was found in each instance. Only two of the cases had clear histories of cranial arteritis.

Granulomatous aortitis must be considered when there is arteritis elsewhere, when there is dilatation of the ascending part or arch of the aorta, and in a variety of other presenting circumstances. It is likely that studies, particularly follow-up of patients with temporal arteritis, may reveal further cases.

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THE ANATOMICAL APPEARANCE IN RHEUMATIC TRICUSPID VALVE DISEASE

BY

ARTHUR HOLLMAN

From the Cardiac Department, University College Hospital

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Although tricuspid stenosis has aroused interest since Duroziez (1868) pointed out its beneficial symptomatic effect on mitral lesions, there have been few detailed descriptions of the anatomy and function of the rheumatic tricuspid valve.

Lewis (1933) stated that " when stenosis is present it is slight, the thickened valve edge forming a fixed ring of considerable size." Taussig (1937) described a single case with a rigid valve opening 7 cm. in circumference. Altschule and Budnitz (1940) studied two cases and stated that the deformity of the valve " causes a considerable degree of valvular incompetence and also varying degrees of stenosis." Smith and Levine (1942) found 32 examples of tricuspid stenosis in 340 autopsy cases of rheumatic heart disease (9·4%) and noted that the degree of stenosis was severe in 11, moderate in 11, and slight in 10. Aceves and Carrol (1947) studied 49 specimens of tricuspid disease and found " true stenosis " in 22 per cent, " pure insufficiency " in 54 per cent, and mixed lesions in 24 per cent; they did not describe the valve anatomy in any detail. Baggenstoss (1953) concludes that insufficiency and stenosis of the tricuspid valve are almost invariably associated, although one or the other may predominate.

The present study was undertaken in an attempt to obtain useful information prior to submitting a patient to tricuspid valvotomy.

The Normal Tricuspid Valve

The tricuspid orifice is placed in the medial and anterior part of the floor of the right atrium and, with the heart in its natural position, the orifice is almost vertical. Of the valve cusps (Fig. 1) the anterior (infundibular) is usually the largest and extends from close to the infundibulum to nearly the lateral margin of the orifice. The posterior (inferior, right) cusp lies in the right and posterior part of the opening. The septal cusp lies close to the septum and forms also part of the posterior margin of the valve; although usually described as the smallest I have been impressed by the size of the septal cusp in normal hearts where it ranges from 3×1 cm. to $5 \times \frac{1}{2}$ cm. Of the main papillary muscles (Fig. 1), the large anterior muscle is inserted into the adjacent margins of the anterior and posterior cusps, the smaller posterior into the posterior and septal cusps, and the small septal muscle into the septal and anterior cusps. The chordæ tendinæ and papillary muscles are thus attached almost in a ring around the tricuspid valve orifice (Fig. 1) and tether the edge of the valve to three different points of the compass.

The cavity of the right ventricle has a roughly three-sided pyramidal shape with the tricuspid orifice set in the right posterior wall. In the roof of the ventricle a thick muscular ridge, the crista supraventricularis (Fig. 2) separates the tricuspid orifice from the infundibulum and thus helps to divide the ventricular cavity into a posterior inflow tract and an anterior outflow tract. The tricuspid orifice projects into the cavity of the right ventricle rather like a funnel and is set an angle of roughly 60° to the outflow tract.

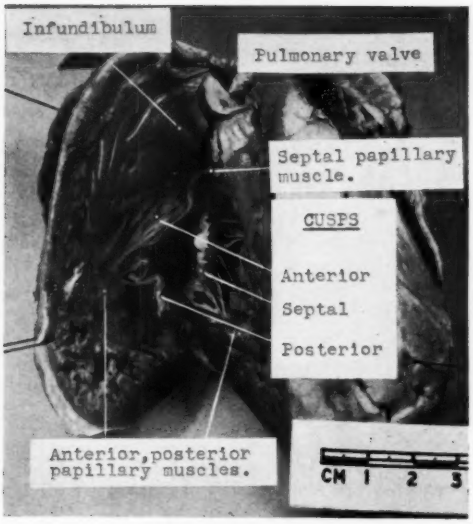

FIG. 1.—The normal tricuspid valve. The chordæ are attached to several points around the circumference of the valve and thus if the chordæ shorten or if the ventricle dilates the cusps will be pulled apart and incompetence will result. Shrinkage of the cusps will similarly lead to incompetence.

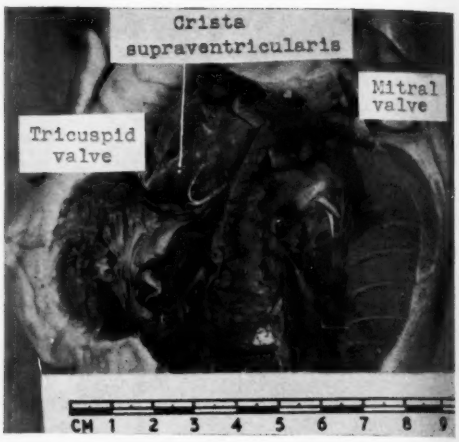

FIG. 2.—Dissection of a normal heart, fixed whole, showing that the tricuspid valve projects into the cavity of the ventricle whilst the mitral valve tends to be flush with the ventricular wall.

The function of the valve may be studied in the dead heart by distending the ventricular cavity with water (Brunton, 1906). Viewed from the right atrium, valve closure is seen to be effected by apposition of the atrial surfaces of the cusps almost at their margins (Fig. 3). The cusps bulge upwards like sails but are prevented from inversion by the chordæ which thus ensure competence of the valve.

The mitral valve, in contrast to the tricuspid, does not project forwards into the ventricular cavity but is set more or less flush with the wall (Fig. 2). In other words the inflow and outflow tracts of the left ventricle are parallel to each other, whereas on the right they are at an angle of about 60°. Therefore, by moving laterally in systole, the anterior cusp of the mitral valve can help to obliterate its inflow tract whilst no such action is possible with the tricuspid valve. In addition, according to Walmsley (1929), the two large mitral papillary muscles actually obliterate part of the inflow tract in systole: there is no comparable muscular action in the right ventricle. It is therefore apparent that the tricuspid valve is anatomically much weaker than the mitral as regards the prevention of incompetence.

THE RHEUMATIC TRICUSPID VALVE

In order to obtain material for this study the museum of every London teaching hospital was visited and a total of 21 specimens of rheumatic tricuspid valve disease was found. The anatomical features of each valve were studied and in addition an attempt was made to assess what the probable function of the valve would have been during life. It is appreciated, however, that estimates of function based on fixed post-mortem material may be inaccurate.

Of the 21 valves, 5 had a valve length of 1·5 cm. or less compared with the normal of 4 cm. and therefore had a moderate or severe degree of stenosis. From the surgical viewpoint these valves are the most important of the group and will now be described.

Moderate and Severe Tricuspid Stenosis. The sizes of the five valves in this group ranged from $\frac{3}{4} \times \frac{1}{4}$ cm. to $1\frac{1}{2} \times 1$ cm. The valve orifice, when viewed from the right atrium, appeared as a circular, oval or triangular hole in a large thin membrane. The orifice was central in four and towards the right and posteriorly in the fifth, where there was dominant fusion of the antero-septal commissure.

With regard to commissural fusion one might have expected from normal valve closure (Fig. 3) that the cusps would be adherent along their atrial surfaces. This type of fusion was in fact found in only one specimen in the entire series of 21; the three fused commissures in this valve are readily made out and have led to a severe degree of stenosis (Fig. 4). In the other four valves in this group the cusps were fused at their adjacent free edges thus producing a continuous valve curtain or shallow funnel, when viewed from the atrial aspect (Fig. 5). With one exception (Fig. 6) it was difficult to see the individual commissures and presumably it would have been difficult during life to palpate them from the right atrium. Well marked commissural fusion, extensive enough to have required division at valvotomy, involved all three commissures in one case, the antero-septal and antero-posterior in one case, the antero-septal and postero-septal in one case, and the antero-septal alone in two cases.

FIG. 3.—Normal tricuspid valve viewed from the right atrium, showing that closure is effected by contact of the cusps along their atrial surfaces. (Ventricle distended with water.)

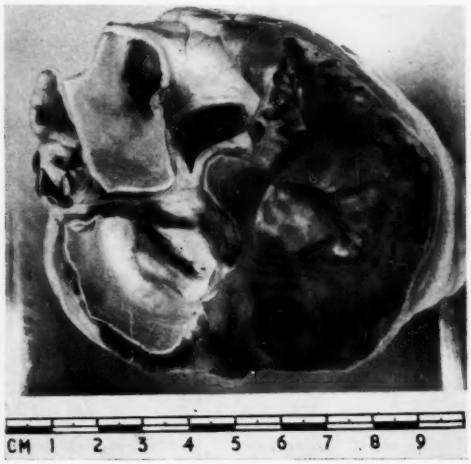

FIG. 4.—Heart divided transversely and viewed from above, showing severe tricuspid stenosis with fusion of the three commissures along their atrial surfaces. Note great dilatation of the right atrium and also the severe mitral stenosis. (Specimen 2393, Gordon Museum, Guy's Hospital. Reproduced by courtesy of Dr. Keith Simpson.)

Viewed from the ventricular aspect the valve appeared as a short funnel with an apparently rigid orifice in four of the five specimens (Fig. 7). The orifice was held open partly by its thickened rim and partly by the pull of the chordæ and papillary muscles from three opposing directions. This short funnel projected forwards into the cavity of the right ventricle and it is difficult to resist the conclusion that the rigid orifice must have permitted the regurgitation of blood through it during life. The probable degree of incompetence was judged to have been slight in one specimen and moderate in three. The fifth valve had dominant fusion of the antero-septal commissure with very little fusion of the other two (Fig. 6), and it seemed likely that in systole the posterior cusp

FIG. 5.—Valve viewed from above, showing the customary appearance in tricuspid stenosis. The valve has been converted into a smooth funnel in which it is almost impossible to make out the commissures.

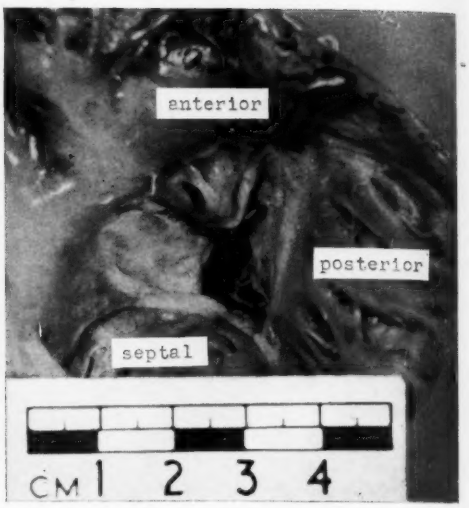

FIG. 6.—Extensive fusion of the antero-septal commissure has produced this fairly severe stenosis. The posterior cusp was probably able to close the orifice and thus prevent incompetence.

could fill the orifice and thus prevent incompetence. Thus of the five valves with moderate or severe stenosis probably only one was competent.

The valve cusps were smaller than normal, the anterior cusp for example averaged 14 mm. from base to free margin compared with a normal of 20 mm. The body of the cusp was sometimes thickened where chordæ were adherent to it, but on the whole the cusps were relatively thin and pliable. Calcification of the cusps was not seen. The free edge of the cusps, however, was considerably thickened in this group.

The chordæ tendinæ usually showed some shortening and thickening and the chordæ that gained insertion into the body of the cusp were sometimes adherent to it. But on the whole the chordæ were not much involved and only one specimen (Fig. 7) showed severe shortening of the chordæ. Cross fusion of the chordæ was never seen and thus sub-valvular stenosis was likewise absent.

Slight or No Stenosis. Of the remaining 16 specimens, 8 had slight stenosis with a valve length of 1·6 to 2·5 cm. and 8 had virtually no stenosis. The general features of these valves were similar to those described for the tightly stenotic ones. The cusps were always fused at their adjacent free edges and in some instances as a result the commissure was so indistinct that its position could only be made out from the insertion of the chordæ.

Eight of the specimens had well-marked fusion of only one commissure which was the antero-septal in seven and the postero-septal in one, and a further specimen had fusion of both. The majority of the 16 specimens looked as though they were incompetent during life and in 8 of them the incompetence was probably considerable in degree.

Involvement of Other Valves. The mitral valve was diseased in all the 21 specimens. In two-

FIG. 7.—Fairly severe tricuspid stenosis with a rigid incompetent valve orifice. The degree of chordal involvement is unusually severe. Compared with the stenosed mitral valve the position of the tricuspid orifice clearly favours incompetence.

thirds it presented the typical appearance of a tight pure stenosis whilst in 6 specimens it appeared to be both stenotic and incompetent, and in one to be dominantly incompetent.

Aortic valve involvement was found in 14 specimens, being moderate to considerable in degree in 12 of these. It was unaffected in 3 and was absent from the specimen in the remainder.

In the specimens studied the mitral valve always contrasted strongly with the tricuspid valve. The mitral valve usually presented the typical appearance of tight mitral stenosis and the valve was well protected from incompetence by a large anterior cusp which was often lengthened by fusion with the chordæ. As can be seen from Fig. 7 this state of affairs was very different from that with the stenosed tricuspid valve where a rigid orifice projected into the ventricular cavity and favoured incompetence. The normal valve anatomy was thus mirrored in the diseased valves.

A Calcified Tricuspid Valve. The heart from a man, aged 46, who died with pulmonary valvular stenosis shows the only calcified tricuspid valve I have seen. The valve cusps were thickened especially at their margins and contained nodules of calcium and the chordæ were shortened. The pulmonary valve orifice measured 3 mm. in diameter and the right ventricle was as thick as the left. The mitral and aortic valves were normal. This may be an example of congenital tricuspid valve disease, or possibly the changes may be secondary to the long continued high closing pressure to which the valve was subject. Rheumatic involvement seems unlikely.

Discussion

The difference in anatomy and function between the mitral and tricuspid valves has been recognized since William Harvey (1628) wrote, "In the left ventricle therefore, and in order that the occlusion may be the more perfect against the greater impulse, there are only two valves, like a mitre, . . . and produced into an elongated cone, so that they . . . touch to their middle. . . . thus it is that these mitral valves excel those of the right ventricle in size and strength and exactness of closing." King, in 1837, found that distension of the ventricle with water always closed the mitral valve firmly whilst the tricuspid often presented a considerable reflux. He thought that the tricuspid valve being weak could act as a safety valve to the right ventricle. The present study has confirmed these anatomical and functional observations on the normal valve and has shown that similar considerations apply to the valve when affected by rheumatic disease.

In this series the ratio with severe, moderate and slight affections was 24, 38, and 38 per cent, a figure similar to that of Smith and Levine (1942). Tricuspid incompetence was thought to be slight or absent in 38 per cent, moderate in 28 per cent, and considerable in 38 per cent. The conclusion from this study that incompetence is a common accompaniment of stenosis of the tricuspid valve is open to the objection that function cannot be accurately deduced from anatomical appearance; but support for this deduction is found in the reported cases of tricuspid valvotomy of which only 25 per cent (2 out of 8) had competent valves at operation (Hollman, 1956).

The antero-septal commissure was fused in this series in 14 instances compared with 6 fusions of the postero-septal and 4 of the antero-posterior commissure (excluding slight degrees of fusion). This dominance is probably due to the fact that the angle between the anterior and septal cusps is much narrower than at the other two commissures and thus these cusps can more readily become adherent to each other (Fig. 1).

Summary

The anatomy of the normal tricuspid valve shows it to be vulnerable to incompetence especially when it is compared with the mitral valve.

Of 21 specimens of rheumatic tricuspid valve disease there were 5 with well marked stenosis. The valve orifice in four of these five formed a short rigid funnel which was probably incompetent during life, but was competent in the fifth. The fused commissures, with a few exceptions, were difficult to see from the atrial aspect and presumably would have been difficult to feel at valvotomy during life. Eight of the sixteen valves with slight or no stenosis were probably incompetent to a considerable degree.

The stenosed mitral valve usually contrasted strongly with the stenosed tricuspid valve in the same specimen in that the mitral valve was clearly much better protected from incompetence.

I am most grateful to the curators of the museums of the London teaching hospitals for permitting me to study and describe specimens in their care. It is a pleasure to thank Dr. Kenneth E. Harris for his help in the preparation of this paper. The photographs were taken by Mr. A. C. Lees and Mr. A. Bligh.

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PULMONARY ARTERIAL PRESSURE AFTER PRISCOLINE IN MITRAL STENOSIS

BY

K. BRAUN, G. IZAK, AND S. Z. ROSENBERG

From the Cardiovascular Laboratory and Department of Internal Medicine (Division 'B'), Rothschild-Hadassah University Hospital, Jerusalem, Israel *

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It has been observed that in certain cases of mitral stenosis the increase in pulmonary arterial pressure is out of proportion to the pressures on the venous side of the pulmonary circulation. This increase is due to narrowing of the pulmonary arterioles (Dexter *et al.*, 1950; Baker *et al.*, 1952; Ferrer *et al.*, 1952), which may result either from organic changes in the pulmonary arterioles (intimal proliferation and medial hypertrophy) (Parker and Weiss, 1936; Larabee *et al.*, 1949) or from increased pulmonary vascular tone due to over-activity of the autonomic nervous system (Holling, 1952; Curti *et al.*, 1953) or both.

Various drugs have been used to determine the influence of the autonomic nervous system on pulmonary hypertension in cases of mitral stenosis. Thus, large decreases in right ventricular pressure (Wilson and Keeley, 1953) and in pulmonary arterial pressure—without decrease in cardiac output—have been observed following the administration of hexamethonium (Davies *et al.*, 1954). Using priscoline Gardiner (1954) observed a fall in the pulmonary arterial pressure in two cases of mitral stenosis.

In the present study priscoline was used to analyse the role played by increased vascular tone in the pulmonary hypertension of mitral stenosis. Priscoline † (2-benzyl 1–4·5 imidazoline hydrochloride) is a sympathicolytic and adrenolytic agent (Chess and Yonkman, 1940) and is thought to cause vaso-dilatation by blocking the sympathetic end-organs in the vessel walls.

Material and Methods

Fourteen patients with predominant mitral stenosis, confirmed at operation, and with various degrees of pulmonary hypertension were studied. None was suffering at the time of the examination from acute pulmonary complications such as pneumonia or pulmonary infarction and none had clinical or laboratory signs of rheumatic activity.

Right heart catheterization was performed in the usual manner (Cournand and Ranges, 1941; Bloomfield *et al.*, 1946). Pulmonary arterial and brachial arterial pressures were recorded simultaneously by an electromanometer on a Sanborn polyvisocardiette. Mean pressures were obtained by electrical integration. Mixed venous blood was withdrawn from the pulmonary artery simultaneously with brachial arterial blood. Oxygen content and capacity were determined by the method of Van Slyke and Neill (1924). Oxygen consumption was measured in four patients with a closed

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† Ciba Pharmaceutical Product, Inc.

spirometer and in eight patients expired air was collected in a Douglas bag and analysed for oxygen and carbon dioxide with a Scholander micro-gas analyser (Scholander, 1947). Blood pressures were recorded and blood samples were obtained before and 2, 10, 20, and 30 minutes after the injection of 25 mg. of priscoline through the catheter. Cardiac output (Fick principle) and pulmonary vascular resistances (Gorlin *et al.*, 1951) were determined before and at 10 and 30 minutes following the injection. In four additional cases of mitral stenosis only pulmonary wedge pressure and simultaneous brachial arterial pressure were recorded before and 10 minutes after administration of priscoline.

Results

Priscoline caused in all patients a transient increase in the pulse rate for about five minutes. This increase ranged from 12 to 20 beats a minute.

In two of the fourteen patients (Cases 13 and 14, Table I) examined, the development of pulmonary œdema 5 minutes following the injection of priscoline prevented the completion of the observation. This occurred without any appreciable fall in the pulmonary arterial pressure being recorded.

TABLE I

Summary of Data obtained 10 Minutes after Injection of Priscoline in 14 Patients

No.	Name	Pulmonary artery (mean) mm. Hg		Brachial artery (mean) mm. Hg		Pulmonary artery O_2 saturation %		Brachial artery O_2 saturation %	
		Before Priscoline	After Priscoline	Before Priscoline	After Priscoline	Before Priscoline	After Priscoline	Before Priscoline	After Priscoline
1	B. A.	75	39	87	83	67·5	75	97	91
2	F. B.	60	43	80	75	48	60	96	76·5
3	S. N.	58	25	117·5	110	74	65·5	102	98·5
4	L. H.	55	40	105	85	65	59	94	88
5	B. N.	37·5	25	100	75	68·5	61	93·5	88
6	C. W.	37·5	25	87·5	63	87	88	102	95
7	F. B.	27	15	75	60	72	73	93·5	90
8	P. B.	26	16	83	—	—	—	—	—
9	R. A.	26	22	80	100	86	76·5	100	96·5
10	D. T.	25	18	58	45	68	72	101	92·5
11	Ch. K.	17	17	90	—	—	—	—	—
12	P. E.	15	14	77	65	67	71	97	91
13	S. D.*	40	36	87	68	67	71	94	97
14	F. R.*	85	80	100	99	55	60·5	90	86

* These two patients developed pulmonary œdema, and therefore the observation had to be interrupted after 5 minutes.

In 11 out of the 12 remaining patients the pulmonary arterial mean pressure decreased following the administration of priscoline, the fall ranging from 7 per cent to 57 per cent of the initial values. In another patient the pulmonary arterial pressure did not change (Table I). Some correlation was observed between the initial height of the pulmonary arterial pressure and the extent of the decrease in this value following the injection of priscoline. The higher the initial pressure, the greater the fall following administration of the drug (Table I). In Cases 9–12, where the initial pulmonary artery pressure was either normal or only slightly raised the drop in pressure following priscoline was small.* The mean pressure in the brachial artery was measured simultaneously with the pulmonary arterial pressure in 10 of the 12 patients. The brachial arterial pressure decreased in 9 patients, the fall ranging from 6 per cent to 25 per cent of the initial values, and increased in one patient by 2 per cent. The maximal effect on the pulmonary and brachial arterial

* This fall in the pressure may be insignificant, since similar changes are within the range of variations during catheterization.

pressures was noted 10 minutes following the administration of the drug. The onset of the fall in the pulmonary arterial pressure preceded that in the brachial artery (Fig. 1).

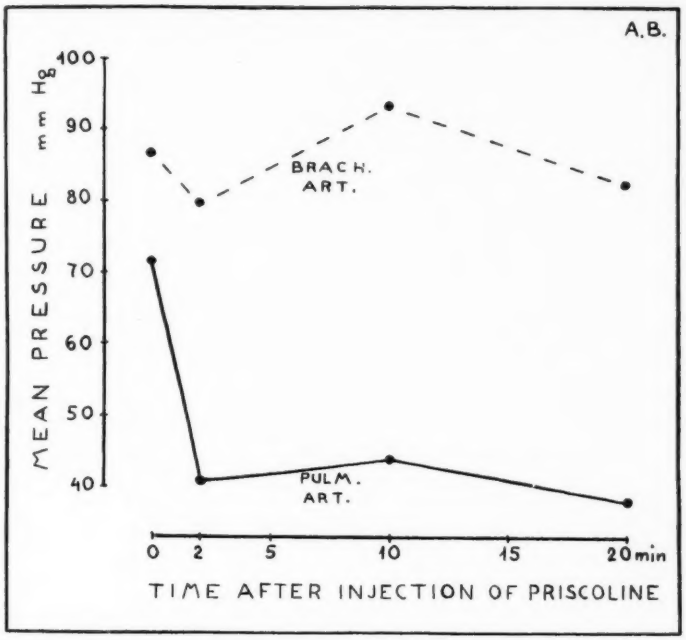

FIG. 1.—Showing the changes in pulmonary arterial pressure and brachial arterial pressure following the injection of 25 mg. of priscoline.

The oxygen saturation in the pulmonary arterial blood changed during the course of the observations, falling in five patients by 3·0 to 9·5 per cent, and rising in the other five patients by 1 to 12 per cent. The oxygen saturation in the brachial arterial blood decreased in all ten patients examined, the fall ranging from 3·5 to 19·5 per cent. There was no relation between changes in the oxygen saturation following the injection of priscoline and initial pulmonary arterial and brachial arterial pressures (Table I).

The cardiac output increased in seven patients (from 1·6 to 5·0 l./min.), remained unchanged in two, and decreased in another patient from 8·9 l./min. to 4·5 l./min., following the administration of priscoline. The pulmonary vascular resistance diminished in nine patients, the decrease ranging from 48 to 1025 dyn. cm.$^{-5}$ sec., and increased in one patient by 118 dyn. cm.$^{-5}$ sec.

In four patients in whom only pulmonary wedge pressures were measured the mean pressure values were 30, 27, 25, and 17 mm. Hg respectively. There was no great change in these values following the injection of priscoline.

DISCUSSION

It has been demonstrated above that pulmonary hypertension in mitral stenosis may be reduced by priscoline, a sympathicolytic agent. Furthermore, the greater the initial pulmonary arterial pressure, the larger the decrease following the injection of priscoline. Since the fall in pulmonary arterial pressure preceded that in the systemic artery, the effect of priscoline on the pulmonary arterial pressure was apparently not secondary to pooling of blood in the peripheral circulation.

Our studies suggest, therefore, that the autonomic nervous system plays an important role in the maintenance of pulmonary hypertension accompanying mitral stenosis, probably by producing increased vasomotor tone in the pulmonary arterioles. These observations confirm those of several other authors who found that priscoline, as well as tetra-ethylammonium-chloride and hexamethonium reduced pulmonary hypertension due to various causes (Davies *et al.*, 1954; Fowler *et al.*, 1950; Dresdale *et al.*, 1954). However, in none of our patients with much pulmonary hypertension did priscoline reduce pulmonary pressure to normal. The residual elevation of the pulmonary arterial pressure may be due to organic changes in the pulmonary vascular tree (Parker and Weiss, 1936; Larabee *et al.*, 1949), to the transmitted back pressure caused by the stenotic valve, or to myocardial insufficiency (Harvey *et al.*, 1949; 1955). The failure of priscoline to lower the pulmonary wedge pressure in four cases suggests that the main effect of the drug is on the tonus of the pulmonary arterioles.

The pulmonary arteriolar spasm found during these observations probably represents an important factor in the causation of the so-called protective pulmonary hypertension which shields the capillaries from an excessive increase in pulmonary blood flow (Wood, 1952). This increase might raise the hydrostatic pressure and eventually lead to the development of pulmonary œdema. However, the pulmonary œdema that appeared in two of our patients after injection of priscoline was apparently not caused by reduction in this protective pulmonary hypertension. In these two cases the pulmonary arterial pressures had not yet fallen appreciably when the œdema developed. The probable cause of this serious complication was the increase in pulse rate after the injection. Since Davies *et al.* (1954) noted that pulmonary œdema develops more frequently in cases of mitral stenosis with excessive pulmonary hypertension, they reject the concept of protective pulmonary hypertension and recommend hexamethonium as a therapeutic agent in these patients. Our series is too small to draw conclusions as to whether priscoline is beneficial or contra-indicated in this condition.

While the changes in the oxygen saturation of the pulmonary arterial blood were not consistent, the peripheral oxygen saturation fell significantly (from 3·5 to 18·5%) in all 10 cases studied. A possible explanation for this is that vasodilation produced by priscoline may increase blood flow in lung segments with poorly ventilated alveoli, thus leading to pulmonary venous unsaturation (Curti *et al.*, 1953; Dresdale *et al.*, 1954; Carrol *et al.*, 1953). Another possibility is that the sudden drop in the pulmonary arterial pressure may change the direction of blood flow in the anastomotic branches connecting the pulmonary and bronchial vascular systems in cases of mitral stenosis (Ferguson *et al.*, 1944). Liebow (1953, 1954) suggested that with an increased shunt between the systemic and pulmonary venous circulation, the valves of the bronchial veins may become incompetent and the blood may flow in either direction according to the development of pressure gradients.

It seems quite probable that the calculated increase in cardiac output, which in some cases was over 4 litres, is incompatible with the degree of mechanical obstruction of the mitral valve found at operation. Rapid changes in the circulatory system during an observation of brief duration may cause large variations in the arterio-venous oxygen difference and oxygen consumption. Therefore the reliability of applying the Fick method in such a case has been questioned (Visscher and Johnson, 1953; Donald *et al.*, 1954). Similarly, the calculated values for vascular resistances in the pulmonary and systemic circulation also appear to be not entirely reliable.

Summary and Conclusion

The effect of priscoline on the pulmonary and brachial arterial pressure and oxygen saturation, on cardiac output and vascular resistances was studied in 14 patients with mitral stenosis. The drug caused a significant fall in pulmonary artery pressure, while the fall in the peripheral arterial pressure was much less pronounced.

Priscoline through its sympathicolytic and adrenolytic effect apparently diminishes pulmonary arteriolar spasm present in cases of mitral stenosis with pulmonary hypertension.

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HÆMODYNAMIC STUDIES DURING AURICULAR FIBRILLATION AND AFTER RESTORATION OF SINUS RHYTHM

BY

OLE JACOB BROCH AND OTTAR MÜLLER

From the Medical University Clinic in Bergen, Norway

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Auricular fibrillation is one of the most frequent rhythm disturbances in organic heart diseases, being present in about 70 per cent of all cases of congestive failure. Sometimes fibrillation is found in young persons with otherwise healthy hearts, as stated already by Mackenzie in 1911; in 651 cases of auricular fibrillation he found no other signs of heart disease in 4·6 per cent. Orgain *et al.* (1936) found this form of fibrillation in 6·5 per cent. Evans and Swann (1954) described this as "lone auricular fibrillation", by which they mean auricular fibrillation without signs of structural heart disease. Conditions for the diagnosis are normal heart size and heart rate and no murmur: the functional capacity and prognosis of the subject are normal.

As a consequence, the regular contractions of the auricles cannot always be essential for the working capacity of the heart. It may, however, represent a less rational way of heart work. In healthy subjects the reserve capacity of the heart is so great that a slight reduction of its efficiency is of minor importance, and will only be noticed under great strain. In the failing heart, however, even a small reduction of the capacity may be of importance. Auricular fibrillation often marks an aggravation of congestive failure in heart disease. However, this is primarily due to the tachycardia or indicates a progression of the heart disease. It is therefore very difficult to separate the effect of the auricular fibrillation *per se* on the symptoms and signs of cardiac patients from the deleterious effect of other factors.

Stewart *et al.* (1928) examined the rate of blood flow during experimental fibrillation in dogs. They found no difference compared to sinus rhythm.

By means of heart catheterization it is possible to study the circulation in man more closely. Ferrer *et al.* (1948) as well as Wade *et al* (1952) compared two groups of patients with rheumatic heart disease, with and without fibrillation, and found (on the average) lower cardiac output in the cases of fibrillation. It is difficult, however, to draw conclusions from a comparison between two small groups of different patients. Kory and Meneely (1951) studied the circulation by heart catheterization before and after the restoration of normal rhythm with quinidine. In six of eight patients they found a considerable increase of the cardiac output both at rest and during exercise after sinus rhythm was restored. Hecht *et al.* (1951) examined 15 patients in the same way: while at rest the mean increase of the cardiac output after the achievement of sinus rhythm was small, the increase during exercise was statistically significant, and the mean pressure in the pulmonary artery found was unchanged. They concluded that "these observations indicate that a coordinate contraction of the cardiac atria aids in cardiac filling during demand periods, and that this reserve function is lost in atrial fibrillation."

Reeve-Hansen *et al.* (1952) studied 14 patients with fibrillation of durations ranging from six months to five years. All patients had been digitalized. From three weeks to two months after restoration of sinus rhythm by means of quinidine the patients were re-examined. In 9 of 14 patients a significant (i.e. more than 10%) increase of the cardiac output at rest was found, while in five

it was unchanged. The peripheral resistance was significantly reduced in nine. The mean arterial pressure showed some variations. The pressure in the pulmonary artery showed no systematic change. They concluded that the results indicated an improvement of the circulation due to the restoration of sinus rhythm by means of quinidine, and they also maintained that a subjective improvement occurred. Storstein and Tveten (1955) confirmed these findings in five patients. These authors have all found a decline in the arterio-venous oxygen difference after restoration of sinus rhythm. Storstein and Tveten suggested that the effect may be due to the peripheral vasodilating effect of the quinidine with a reduction of the peripheral resistance. According to investigations by Ferrer *et al.* (1948) no unequivocal hæmodynamic changes have been found after quinidine medication to indicate that the drug is the cause of all the changes found after conversion to sinus rhythm independent of the sinus rhythm *per se*.

The findings in these investigations vary so much that further observations are necessary to reach reliable conclusions.

Material and Methods

Twenty patients (14 men and 6 women) were examined by heart catheterization before and after restoration of normal rhythm with quinidine. Eleven suffered from mitral stenosis, in five combined with aortic valve disease, four had coronary heart disease, two were of unknown origin, one had thyrotoxicosis, and one lone auricular fibrillation.

The degree of functional capacity was assessed on admittance according to the New York Heart Association's classification. Thirteen belonged to groups I and II, 5 to group III, and 2 to group IV.

All patients had been digitalized for a long time and had spent a sufficiently long period in the ward for the circulation to stabilize. None of them had noticeable congestive failure with œdema before the investigations were started. They had toilet privileges, but were otherwise confined to bed.

Restoration of normal rhythm was carried out with doses of quinidine sulphate increasing from 1·2 g. to as much as 3·6 g. daily. Two suffered relapses, but were later converted to sinus rhythm after a second attempt. The majority of the patients were kept on a maintenance dose of 0·8 g. per day after the conversion, a few somewhat less. In the last seven patients the quinidine medication was stopped for some days before the second catheterization. Otherwise the treatment was the same before and after restoration.

During the heart catheterizations, pressures were recorded in the right atrium, the pulmonary artery and in the pulmonary artery wedge position, and blood samples obtained from a pulmonary and a peripheral artery with the patient resting on the table. The same pressure recordings and blood samples were obtained during exercise on a bicycle ergometer with a fixed resistance, except for observations from the right atrium. The second catheterization was performed after sinus rhythm had lasted from a minimum of four days up to three months, usually after a period of from one to two weeks.

The exercise tests were carried out as uniformly as possible, during auricular fibrillation and sinus rhythm. It was impossible to obtain all the planned observations in all patients. Particularly during the exercise test some blood samples and pressure registrations failed.

The oxygen consumption was determined by means of Douglas bags, and the cardiac output according to the direct Fick principle. For the pressure registrations Tybjærg-Hansen's manometer was employed. The work of the right ventricle against pressure was calculated according to the formula:

$$RV.W = \frac{CO \times 1{\cdot}055 \times (PAP - RAP) \times 13{\cdot}6}{1000}$$

where PAP is the pressure in the pulmonary artery, RAP the pressure in the right atrium and CO the cardiac output. Only mean pressures are reported.

Results

The results are shown in Table I where the mean values during auricular fibrillation are compared with the findings after conversion to sinus rhythm. A statistical analysis of the observations is also given. Only those cases in which comparable values were obtained are included. An evaluation of the work of the right ventricle during exercise was not possible as pressure measurements in the right atrium were carried out only at rest.

TABLE I

Results of Statistical Analysis

	n	m		x	S	t	P
Cardiac output (l./min.)		A.F.	S.R.				
Rest	17	5·6	6·2	−0·63	0·84	−3·0	0·01 *
Exercise	11	6·8	8·1	−1·52	0·99	−4·85	0·001 *
Stroke volume (ml.)							
Rest	18	66	78	−11·89	19·07	−2·57	0·02 *
Exercise	9	51	69	−15·78	27·06	−1·65	0·15
O_2 consumption (ml./min.)							
Rest	19	257	269	−12·37	37·79	1·39	0·20
Exercise	13	527	537	10·31	11·08	0·32	0·80
Arterial O_2 saturation (%)							
Rest	19	95·9	95·7	0·23	2·06	0·48	0·70
Exercise	6	94·9	95·1	−0·17	2·43	−0·15	0·90
O_2 saturation, pulmonary artery (%)							
Rest	19	71·8	73·6	−1·89	3·06	−2·63	0·02 *
Exercise	16	57·6	60·9	−3·31	5·58	−2·30	0·03 *
Arterio-venous O_2 difference (vol. %)							
Rest	20	4·9	4·15	6·0	8·53	3·09	0·01 *
Exercise	20	7·4	6·3	10·7	15·92	2·93	0·01 *
Pulmonary artery pressure (mm. Hg)							
Rest	19	20·7	21·8	−1·08	4·89	−0·94	0·30
Exercise	17	30·5	32·8	−2·32	5·76	−1·61	0·10
Pulmonary capillary pressure (mm. Hg)							
Rest	16	12·0	14·4	−2·44	3·76	−2·51	0·03 *
Exercise	12	21·9	25·1	−3·5	6·12	−1·90	0·09
Right ventricular work (kg./min.)							
Rest	16	1·35	1·64	−0·29	0·34	−3·3	0·01 *

n=comparable numbers of patients.
m=mean values.
x=mean difference.
−=lower values in auricular fibrillation.
S=variance of the difference.
t=Student's t-test $\frac{\bar{x}}{S}\sqrt{n-1}$.

*=the difference is of statistical significance.
P=level of significance
S.R.=sinus rythm.
A.F.=auricular fibrillation.

As might be expected in investigations where the analytical errors are not inconsiderable, variations in both directions were found. However, most of the observations show clear trends in the variations of the hæmodynamic conditions after restoration of sinus rhythm, and some definite conclusions may be drawn. The cardiac output increases in the great majority of cases, particularly during exercise. In two cases the increase at rest was great and might be due to analytical errors. They are therefore not included in the statistical analysis.

As might be expected, the increase in cardiac output found was due to an increase of the stroke volume. The oxygen consumption remained practically unchanged. Likewise, there was no

clear trend in the variation of the arterial oxygen saturation, neither at rest nor during exercise. After conversion to sinus rhythm there was in most cases an increase of the oxygen content of blood samples from the pulmonary artery with a corresponding reduction of the arterio-venous oxygen difference both at rest and during exercise. There was no difference in the pressure in the pulmonary artery, but some tendency towards a moderate increase of the pulmonary capillary pressure both at rest and during exercise. The work of the right ventricle clearly increased at rest. Right ventricular work during exercise could not be calculated. However, the greater increase in cardiac output during exercise than at rest, and the constancy of the pulmonary artery pressure indicate a correspondingly greater increase in this work during exercise.

Discussion

The increase in cardiac output and stroke volume indicate that sinus rhythm represents a more efficient working of the heart than auricular fibrillation with a greater filling of the ventricles, possibly owing to the auricular activity. The striking increase of the arterio-venous oxygen difference and the decrease in oxygen saturation in mixed venous blood during fibrillation means that, because of a reduced circulation, the peripheral tissues are kept under poorer conditions with regard to oxygen supply and tensions than during sinus rhythm. The improved peripheral conditions during sinus rhythm are at the expense of an increase in the load on the heart, here expressed as a significant increase in work against pressure, and a raised pulmonary venous (capillary) pressure.

To investigate the possible effect of quinidine on the circulation beyond that due to correction of arrhythmia, this drug was withdrawn for some days before the second catheterization in the last seven patients. A statistical analysis showed no difference between this group and the rest of the patients except with regard to the arterio-venous oxygen difference at rest. Those who were given quinidine continuously showed a greater difference after conversion to sinus rhythm ($P : 0{\cdot}05$). Thus there can be hardly any doubt that the hæmodynamic changes demonstrated are due to the restoration of sinus rhythm.

Of the patients examined about half suffered from mitral stenosis. These on the whole had a greater reduction of functional capacity than the others. The patients with mitral stenosis have been compared with the rest of the material in order to see whether they reacted differently to the restoration. Only two observations showed a difference of statistical significance between the two groups. The group with mitral stenosis, compared with the rest, showed after restoration of sinus rhythm: (1) a greater increase in stroke volume at rest ($P: 0{\cdot}001$) and during exercise ($P: 0{\cdot}05$), and (2) less increase in the oxygen saturation in the pulmonary artery at rest ($P: 0{\cdot}05$). It accordingly does not appear as if a transition from auricular fibrillation to sinus rhythm gives changes of greater importance for the circulatory dynamics in cases of mitral stenosis than in fibrillation from other causes.

The investigations show with certainty that a change in the hæmodynamic conditions takes place after resumption of sinus rhythm. That this is favourable for the peripheral circulation cannot be doubted, even if some patients may show a fairly large increase of the pulmonary capillary pressure, particularly during exercise.

To a heart with great functional capacity these changes are certainly of no particular importance. In a subject with an otherwise healthy heart abolition of an existing auricular fibrillation may hardly cause a subjectively noticeable improvement of his functional capacity. To the failing heart, however, the clearly demonstrated changes in the working capacity of the heart may be of great importance.

As far as possible our therapy should therefore aim at achieving sinus rhythm. However, one must be aware that the pulmonary capillary pressure, particularly during exercise, may rise seriously. In three patients the mean pressure during exercise increased by 10·5, 11, and 12 mm. mercury and reached levels where the danger of pulmonary œdema is considerable (Gorlin *et al.*, 1951).

Summary and Conclusions

Twenty patients with auricular fibrillation due to various causes have, after preliminary treatment with digitalis, been catheterized and the circulation studied. After restoration of normal rhythm with quinidine, catheterization has been repeated. The oxygen consumption was essentially unchanged, likewise the arterial oxygen saturation. The other results showed that cardiac output and stroke volume increased both at rest and during exercise after restoration of sinus rhythm. Simultaneously, the oxygen content of the pulmonary artery blood increased, and the arterio-venous oxygen difference decreased considerably. The pressure in the pulmonary artery remained unchanged, but the pulmonary capillary pressure rose after conversion to sinus rhythm both at rest and during exercise, the increase during exercise being not statistically significant. A reduction of the pulmonary vascular resistance was therefore highly probable. The work performed by the right ventricle at rest increased noticeably.

In seven patients the quinidine was withheld for some days before the last catheterization. These patients reacted in about the same way as the others. The only difference of statistical significance was in the arterio-venous oxygen difference at rest. Those who were given quinidine continuously showed a greater difference after regaining sinus rhythm. The quinidine is accordingly not the cause of the hæmodynamic changes observed after transition from auricular fibrillation to sinus rhythm has occurred.

Eleven patients with mitral stenosis were compared with the remaining nine patients. The changes observed were the same, except that in mitral stenosis the stroke volume showed a greater increase at rest and during exercise and the oxygen saturation of mixed venous blood less increase at rest after conversion to sinus rhythm.

Our conclusions are that the circulation improves after the restoration of sinus rhythm, but that the pulmonary capillary pressure in some cases increases to an unfavourable degree.

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PROGNOSIS OF CORONARY HEART DISEASE IN MEDICAL PRACTITIONERS

BY

J. N. MORRIS, J. A. HEADY, and R. G. BARLEY

From the Social Medicine Research Unit of the Medical Research Council, London Hospital, and the Medical Sickness, Annuity and Life Assurance Society

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One of the obstacles to producing general summaries of the prognosis in coronary (ischæmic) heart disease is that it is exceedingly difficult to judge the degree to which any personal or hospital series is representative of the totality of cases, with the widely varying seriousness that does in fact occur (Friedberg, 1949; Katz *et al.*, 1949; Master *et al.*, 1936; Parkinson and Bedford, 1928; Schnur, 1953; Sigler, 1951; Metropolitan Life Insurance Company, 1953; Tudhope and Donald, 1953; White, 1926). Thus, more than half of all deaths from " coronary thrombosis " among middle-aged men are " sudden deaths " and other rapidly fatal *first* clinical attacks (Morris *et al.*, 1952). But such cases, whose inclusion or omission obviously can determine any picture of the prognosis, are quite commonly seen only by general practitioners and coroner's pathologists. This is the kind of situation in which the epidemiological method—aiming to observe all cases in a defined population—can help to complete the clinical picture: each type of case is represented in the experience being analysed in correct proportion (Morris, 1955).

A study based on this principle (though it was not clearly stated there) has already been reported by us and the present study is an extension of it. All male medical practitioner members aged 40–64 years of the Medical Sickness, Annuity and Life Assurance Society, Limited, holding non-cancellable sickness insurance, who suffered a first clinical attack of coronary heart disease between Jan. 1, 1940 and Dec. 31, 1952, were followed up to Dec. 31, 1954. The original study has thus been extended in three ways.

(1) The 73 first attacks occurring in 1951 and 1952 have been added, to make a total now of 316.
(2) The period of observation has been lengthened by $3\frac{1}{2}$ years.
(3) Membership of the Society ceases usually at 65 years of age, and sometimes at 60. In the present study, through the ready co-operation of the General Medical Council, all members no longer on the Society's books were traced till their death or to the end of 1954. There are, thus, no lapses due to loss of contact with cases before the end of the period of observation.

In the previous paper some detailed information is given about the Society and its membership, about the methods of defining and recording morbidity and mortality, and so on. Since this paper is readily available there will be little further reference to such matters. Similarly, the method of estimating the prognosis is described in Appendix 2 of that paper. Readers interested in setting up a prognosis study might refer also to Berkson and Gage (1950), Hill (1955), and Merrell and Shulman (1955).

Results

Table I assembles the data in two ways, (A) describing the mortality at different periods, and (B) the survival rates: it is the obverse of (A). All times are reckoned from the first day of the first clinical attack. the first clinical attack being regarded as the first absence from work, lasting

at least a week, on account of any recognized manifestation of coronary heart disease. The results are presented in three forms (Table I).

(1) All 316 first attacks occurring in 1940–52 (and whatever the detailed diagnosis) are analysed together.

(2) The 252 of the 316 cases where the final diagnosis in the first clinical attack was " coronary thrombosis " (i.e. coronary occlusion or coronary thrombosis or myocardial infarction) are analysed separately.

(3) Similarly, the 52 cases where the final diagnosis in the first attack was *angina pectoris* or *of effort* (ascribed to coronary artery disease or *not* ascribed to any other condition) are also reported by themselves. The prognosis in this angina group is so different from the others that it seemed wise to separate it despite the small numbers.

A group of cases (12 in all of the 316) where the final diagnosis of the first attack was coronary insufficiency, etc., will not be considered further.

TABLE I.

PROGNOSIS FOR LIFE AND DEATH IN CORONARY HEART DISEASE

Male medical practitioners aged 40–64 years. First attacks occurring in 1940–52

(A) CUMULATIVE PROPORTION DYING WITHIN VARIOUS PERIODS FROM THE ONSET OF THE FIRST CLINICAL ATTACK

Mode of presentation	Number of cases	Percentage dying* before the end of the:—												
		1st week	1st m'th	1st year	2nd year	3rd year	4th year	5th year	6th year	7th year	8th year	9th year	10th year	11th year	12th year
All first attacks—all manifestations	316	24	29	32	35	39	41	46	51	56	*59*	*59*	*63*	*63*	*63*
First attacks of coronary thrombosis	252	30	36	40	43	45	48	51	*54*	*58*	*60*	*61*	*65*	*65*	*65*
First attacks presenting as angina pectoris	52	0	0	2	6										

(B) PROPORTION SURVIVING

Mode of presentation	Number of cases	Percentage surviving* to the end of the:—												
		1st week	1st m'th	1st year	2nd year	3rd year	4th year	5th year	6th year	7th year	8th year	9th year	10th year	11th year	12th year
All first attacks—all manifestations	316	76	71	68	65	61	59	54	49	44	*41*	*41*	*37*	*37*	*37*
First attacks of coronary thrombosis	252	70	64	60	57	55	52	49	*46*	*42*	*40*	*39*	*35*	*35*	*35*
First attacks presenting as angina pectoris	52	100	100	98	94										

Data in Text, Tables, and Figures refer to male members of the Medical Sickness, Annuity and Life Assurance Society, Limited. All men included held non-cancellable sickness and accident insurance of a type providing benefit from the beginning of periods of absence from work because of sickness which lasted seven days or more. The members of the Society are mostly resident in the United Kingdom, though there are a few elsewhere.

The figures in italics are less reliable than the others—see footnote to text.

* The percentages are calculated on a " life-table " basis.

No case was labelled until all the information about the first attack was available; in all cases the most serious diagnosis in this illness (or absence) was accepted.

Prognosis in Coronary Heart Disease. The top line of Tables I(A) and I(B) describes the experience with all recognized clinical manifestations of coronary heart disease included.

Prognosis of "Coronary Thrombosis". The second line of Tables I(A) and (B) deals with the "coronary thrombosis" group of cases. Thirty per cent of these male medical practitioners aged 40–64 (Table IA) died in the first week of their first clinical attack. There is good reason to suppose that they died in the first few days of their illness, but the information on this point is incomplete. Seventy per cent, thus, survived the first week (Table I B, second line). In the next few weeks mortality was much lower, though still high, and by the end of the first month another 6 per cent had died. Thereafter the course was quite different. A further 4 per cent died in the remaining 11 months of the first year, and up to 4 per cent annually afterwards till the end of the twelfth year (Table IA, Fig. 1).

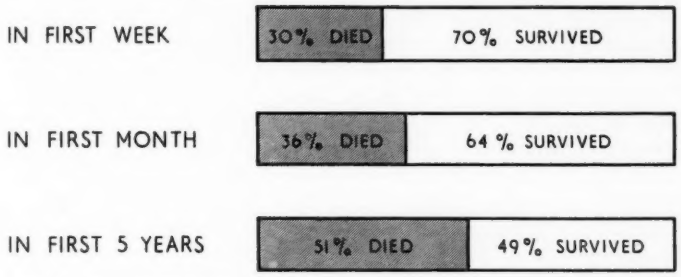

FIG. 1.—Showing the mortality at periods ranging from one week to five years, among male medical practitioners aged 40–64 with coronary thrombosis. The first attacks in this series occurred in the period 1940–52.

These figures, though the experience involved is large, are only reliable within limits. They are all subject to quite substantial "random" error; i.e. the next 252 cases may well show a somewhat different record due to chance effects alone. For practical purposes, however, it is safe to say, on the basis of the figures presented, that, in any similar group of men aged 40–64, the proportion dying in the first week of the first clinical attack of "coronary thrombosis" might be expected to be within 5 per cent of the 30 per cent given in Table IA—i.e. between 25 per cent and 35 per cent. The proportion dying within 5 years was 51 per cent in the experience reported; and again the figures to generalize with would be 46 per cent to 56 per cent. After 5 years the number to be added on each side of the number given in the table becomes a little larger.*

Angina Pectoris. The outlook in this group is very much better. Two per cent of the men first presenting merely with angina (i.e. the final diagnosis in the first illness or absence was angina) died by the end of the first year (Table IA, lowest line); compared with 40 per cent of the men whose first clinical manifestation of the condition was as major occlusion or infarction.

Non-Coronary Deaths. In all there were 166 deaths among the 316 cases being considered, and these 166 were used in calculating the rates which form the basis of Tables I(A) and I(B).

* 25%–35%, 46%–56%, etc., are the 90% "confidence intervals" or *limits*. Regarding the 252 cases that were observed as a sample of the "true" experience, it can be inferred that the proportions dying within the specified times—e.g. 1 week, 5 years, etc.—lie within the *limits* stated. This inference stands a 90 per cent chance of being correct. The narrowness of the limits within which it is possible to make such a statement depends on the numbers of cases available. There are, of course, fewer people who have been followed for a long time after the first attack than for a short time, and hence the confidence that can be attached to the figures in the table declines as the number of years after the first attack increases. For this reason the figures in Table I which can be stated, with 90 per cent confidence, to lie within 5 per cent of the "true" figure are given in ordinary type; while those which cannot be regarded with this degree of confidence are printed in italics. No figures in the table, however, have confidence limits greater than 7 per cent on either side.

Included in the 166 are 15 deaths certified as from conditions unrelated to the present problem (e.g. various cancers), and 2 deaths where the cause is unknown. This makes 17 deaths in all where it is safer to assume that the death was not due to coronary heart disease and its complications; or to assume at any rate, that coronary heart disease did not play the major part in causing death. These cases are too few appreciably to affect the picture given of the prognosis in coronary thrombosis —they accounted for 7 per cent of the deaths in these men—but 7 of the 17 occurred in men where the mode of presentation was angina pectoris; and 5 of these 7 deaths occurred in the first 3 years from the onset. Since the total number of deaths in the 52 men of this angina group during the period of observation was 22, it is obvious that the non-coronary deaths have considerably modified their prognosis. Nevertheless, even with these non-coronary deaths included, as they are in Table I, the prognosis in the angina group is materially better, for the two years that can usefully be reported, than in the cases with a diagnosis of coronary thrombosis.

The Experience at Different Ages. The *trend with age* was irregular in the first week in the coronary thrombosis group (Table II), but was clear by the end of the first month (Fig. 2): the

TABLE II

PROGNOSIS FOR LIFE AND DEATH IN CORONARY THROMBOSIS

Variation with age at onset of clinical disease. Male medical practitioners

First attacks occurring in 1940–52

Age at onset of first attack	Number of cases	Percentage surviving to the end of the:—						
		1st week	1st month	1st year	2nd year	3rd year	4th year	5th year
40–49	78	74	71	69	68	62	61	56
50–54	65	69	65	62	58	58	56	53
55–59	60	63	58	53	50	48	44	42
60–64	49	69	57	53	47	45	43	40

These percentages are subject to a considerable random error because of the small numbers involved, and generalizations from them can only be approximate. The general tendency for the percentage surviving for a particular period (e.g. 2 years) to decrease with advancing age is, however, most unlikely to be a chance effect (coefficient of concordance $W=0{\cdot}89$, $P<0{\cdot}001$).

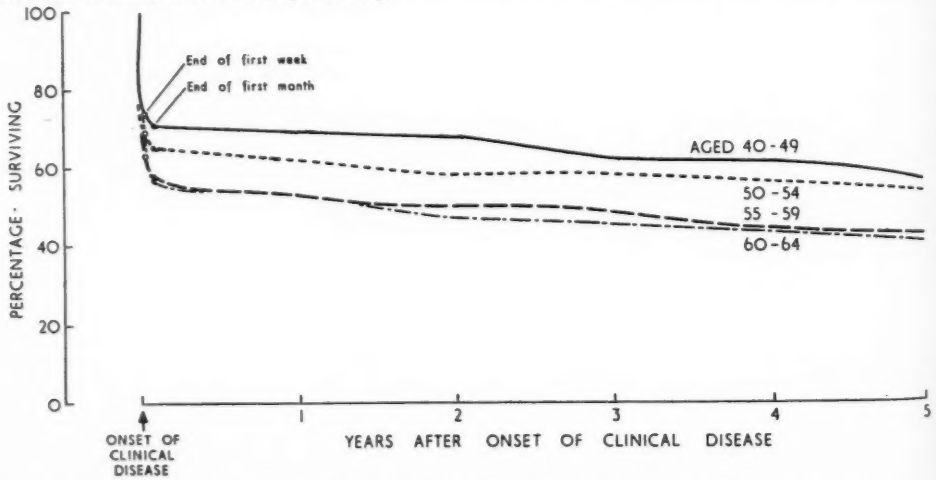

FIG. 2.—Showing the relation between age of onset of coronary thrombosis and length of life in male medical practitioners during the five years following the onset. First attacks in this series occurred in the period 1940–52.

prognosis is somewhat better when the age at clinical onset is 40–49 years than 60–64 (71 per cent surviving the first month in comparison with 57 per cent; 69 per cent surviving the first year against 53 per cent, and so on). This analysis is presented only for the coronary thrombosis group, but the trends are the same when all manifestations are taken together and the total 316 cases broken down by age. The figures in this table are, of course, much less reliable than those in Table I because the numbers of cases in each age-group is relatively small. There is, however, no doubt that the *trend* for mortality to be less among men in their forties is " significant " and most unlikely to be a chance effect. However, death rates in general tend to be lower at younger ages, and the advantage at 40–49 years which is seen in Table II is substantially less than usually found when the general mortality experience of men in their forties is compared with that of men in their early sixties.

Changes Between 1940–46 and 1950–52

No information is available about the mode of treatment of the individual patients. However, it may be interesting that the cases of coronary thrombosis first presenting in 1950–52 did a little (though not significantly) better than those of 1940–46. The following figures are a fair summary of the data.

Chances of Surviving: Male Medical Practitioners Aged 45–64 with Coronary Thrombosis

	Percentage surviving to the end of the:—						
Year of first clinical attack	1st week	1st month	1st year	2nd year	3rd year	4th year	5th year
1940–46	64	57	53	48	47	45	43
1950–52	73	68	64	62	58	56	51

Deaths from all causes are included in this analysis; but the cases aged 40–44 years have been excluded because of special problems of this group that will be discussed elsewhere. There were 77 first attacks in 1940–46, in men aged 45–64, and 90 in 1950–52. The fact that there were more in the three recent years than in the seven years, 1940–46, is an illustration of the increase of coronary heart disease among middle-aged members which is the most striking feature of the recent morbidity experience of this Society (Morris *et al.*, 1952). There was a rise in the number of members between 1940 and 1952, and some rise in their average age during this period; nevertheless the number of first attacks in 1950–52 would have been very much nearer 40 than 90 if there had been no increase in incidence of the disease, or, at least, in its recognition. It is probable that more cases of ischæmic heart disease that were mild or uncharacteristic were being diagnosed in 1950–52 than in the early 1940s; and this may be improving the outlook of the 1950–52 cases as a whole as well as almost certainly playing a part in increasing the total number certified (Morris, 1951, 1955). However that may be, it seems that if better treatment had anything to do with slightly better prognosis in 1950–52 this must have been effective in the first hours and days of the first clinical attack—e.g. in terms of anti-shock measures—because such improvement as did occur was apparent in the first week, with 73 per cent surviving it in 1950–52 compared with 64 per cent in 1940–46.

Summary and Conclusions

The information presented illustrates how the epidemiological method (Morris, 1955), counting all defined cases occurring in a counted population, can help to increase the accuracy of general numerical summaries of the prognosis in such conditions as coronary heart disease. For example, deaths in the first few days of the first clinical attack dominate the picture of mortality in this disease. Thirty per cent of these men who had first clinical attacks diagnosed as coronary occlusion or coronary thrombosis or myocardial infarction died in the first seven days of their illness and a further 30 per cent in the next 7, 8, or 9 years. If the correct proportion of these early malignant, rapidly fatal cases is not included in any series, the picture presented by the series will be unduly

optimistic or pessimistic. Indeed, so much happens from hour to hour and day to day at the beginning of the first clinical attack that it is probably safer not to make any overall statements about the long-term prognosis in coronary thrombosis before the end of the first week of the illness. This does not apply to statements about the outlook in particular defined clinical types (Gilchrist and Tulloch, 1956; Morgan Jones, 1955; Russek and Zohman, 1952). The outlook among the survivors of the first week is relatively good, and is given in convenient form in Table III which thus supplements Tables I and II whose main results are also summarized in the top part of Table III. About 70 per cent of the survivors of the first week survived another 5 years; about 50 per cent survived 10 years. (The reader can easily make the necessary calculations for coronary heart disease as a whole—all first clinical manifestations among these doctors—from Table I.) In passing, it may be remarked that hospital series will usually represent experiences intermediate between those from the beginning of first clinical attack (e.g. Table I), and those from the end of first week (e.g. Table III).

TABLE III

SURVIVAL RATES AT THREE STAGES OF THE FIRST CLINICAL ATTACK OF CORONARY THROMBOSIS

252 male medical practitioners, aged 40–64 years suffering a first clinical attack in 1940–52

Stage	Age at first attack	Proportion surviving 5 years	Proportion surviving 10 years
From the beginning of the first clinical attack ..	40–64	49%	35%
	40–49	56%	
	50–59	48%	
	60–64	40%	
From the end of the first week of the first attack	40–64	70%	50%
	40–49	75%	
	50–59	72%	
	60–64	58%	
From the end of the first month of the first attack	40–64	76%	55%
	40–49	79%	
	50–59	77%	
	60–64	70%	

The percentages for all ages together, 40–64, should if used for generalization, be quoted as " 44–54% " and not " 49% ", etc. The percentages for individual age groups are subject to a considerable random error.

We are greatly obliged to the Directors of the Medical Sickness, Annuity and Life Assurance Society, Limited, and to Mr. E. A. J. Heath, General Manager of the Society; to the General Medical Council and their staff; to the Registrar General; and to Mrs. V. P. Hall, computer, and Mrs. I. R. Murray, secretary of the Social Medicine Research Unit.

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SEPTAL INFARCTION WITH RECOVERY OF THE ELECTROCARDIOGRAM

BY

D. GORDON ABRAHAMS*

From the Medical Unit, the London Hospital

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The different electrocardiographic patterns that are associated with infarction of various parts of the heart are widely recognized today. This knowledge has been acquired from numerous studies correlating the electrocardiograms recorded during life with the position of the pathological changes found in the heart at necropsy. In general the management and prognosis of cardiac infarction depends upon the extent of the damage sustained by the heart; the anatomical site of infarction seems to be relatively unimportant in this respect. The description of yet another " type " of cardiac infarction would therefore appear to be of little practical importance.

Recently, however, several patients have been observed in whom unusual electrocardiographic features were associated with the infarction of a particular part of the heart—namely the interventricular septum. The clinical features of these patients were also rather unusual in certain respects. Five such patients are described in this paper; in each instance chest pain was accompanied by an abnormal electrocardiogram, so that a diagnosis of cardiac infarction was made. All the electrocardiograms showed a consistent and distinctive pattern; the initial abnormalities were similar, and the subsequent behaviour was surprising, for all reverted to normal leaving no trace of the previous infarction. Two of the patients died later, and post-mortem examinations were made. From an analysis of the case histories, clinical findings, electrocardiograms, and the available evidence at necropsy, certain facts have emerged that seem worth recording.

Clinical Features

It is not proposed to discuss the clinical features of the individual cases in detail but a summary of the relevant facts is provided in Table I.

There was nothing to suggest a common familial tendency towards heart disease in the members of the group. There were four men and one woman in the series—a distribution that reflects the usual sex incidence of cardiac infarction. Their ages, when first seen, ranged from sixty-six to forty-seven years with an average of just under fifty-five years. High blood pressure was not a prominent finding, for only one patient (Case 3) had persistent hypertension, and one other (Case 1) transient hypertension of short duration. In only one (Case 3) was heart disease recognizable by clinical methods.

All members of the series had pain in the chest at one time or another. In two patients this was typical cardiac pain, but in the others the pain was atypical, and in these three the electrocardiographic findings were unexpected. It is also worthy of note that none of the patients has suffered subsequent attacks of angina pectoris during the period of follow-up.

A most interesting and prominent feature was the frequency of associated gastro-intestinal disease and symptoms. Thus one man (Case 2) was a life-long dyspeptic, and suffered a perforated ulcer about eighteen months before his first attendance. In another man gastrectomy had to be

* Now Senior Lecturer, Dept. of Medicine, University College, Ibadan, Nigeria.

performed for intractable peptic ulceration (Case 5). Cholecystectomy was necessary in a third for recurrent gall-bladder colic (Case 3). A fourth (Case 1) suffered from minor attacks of indigestion for which no cause could be found, and only one (Case 4) was free from digestive symptoms. The presence of demonstrable disease in the gastro-intestinal tract, occurring as it did in the majority of the patients, complicated the clinical picture and rendered an accurate clinical diagnosis extremely difficult in some instances.

The chest pain was accompanied by signs of circulatory disturbance in only one patient—an elderly woman who had recently undergone cholecystectomy (Case 3). None of the others showed any signs of cardiac insufficiency, and the majority did not even seem to take their pain very seriously.

Two patients (Cases 4 and 5) died after three and twenty-two months observation respectively. The three survivors have been watched for periods of from twenty to forty-four months; all are enjoying a normal, unrestricted life. No patient has had a recurrence of symptoms and their electrocardiograms have remained normal.

TABLE I

CLINICAL FEATURES OF FIVE PATIENTS IN SEPTAL INFARCTION

Case No.	Sex	Age*	Chest pain†	Signs of heart disease	B.P.	Associated disease	Period of observation	Present status
1	M	47	Atypical	Absent	170/120 140/80	Acute nephritis. " Minor " dyspepsia	44 months	Symptom free
2	M	56	Atypical	Absent	140/80	Major dyspepsia. Perforated duodenal ulcer 1952	22 months	Symptom free
3	F	66	Typical	Present	235/160	Gall-stones. Cholecystectomy. Hypertensive heart disease	26 months	Well on hypotensive therapy
4	M	55	Atypical	Absent	155/95	Venous thrombosis in the legs	3 months	Dead
5	M	50	Typical	Absent	130/80	Claudication. Gastrectomy for gastric and duodenal ulceration (1954)	22 months	Dead

* Age when patient first came under observation.
† Classified according to criteria for cardiac pain based on the site of the pain, its duration, character, relation to exertion, and relief by rest.

ELECTROCARDIOGRAMS

The electrocardiograms of all patients were remarkably similar during the period when abnormalities were observed, and presented three distinctive features. Pathological Q waves were never present, the S–T segment was always iso-electric, and all abnormalities were confined to T wave changes. The most important characteristic was the complete return to normal subsequently. Similar electrocardiograms were reported by East and Oram (1948) and by Evans (1955), and these authors attributed the transient changes to myocardial ischæmia from coronary artery spasm.

The T wave changes were most apparent in the chest leads—in fact T wave inversion in CR4 was invariable. From this position, which is over the interventricular septum and roughly about the middle of the heart, the T wave inversion extended either to the right involving CR1, or to the left so that CR7 was affected. In one patient (Case 2) the T wave was diphasic in both CR1 and CR7 so that the cardiac damage was evidently more extensive. T wave inversion in the standard limb leads usually accompanied these changes in the præcordial leads, but sometimes the distribution of changes in the limb leads was surprising. Thus, although the præcordial leads always suggested that the

anterior surface of the heart was affected, on one occasion (Fig. 3) the limb leads suggested that the lesion was posterior. A possible explanation lies in the distribution of the coronary arteries that supply the septum.

The distribution of T wave changes in these patients is summarized in Table II and a typical tracing is illustrated in Fig. 1.

TABLE II

ABNORMALITIES OF T WAVES IN ELECTROCARDIOGRAMS OF FIVE PATIENTS WITH SEPTAL INFARCTION

Case	Standard leads			Præcordial leads		
	I	II	III	CR1	CR4	CR7
1	T↓	T↓			T↓	T↓
2	T↓			Diphasic T	T↓	Diphasic T
3	T↓	T↓			T↓	T↓
4		T↓	T↓	T↓	T↓	
5				Diphasic T	T↓	

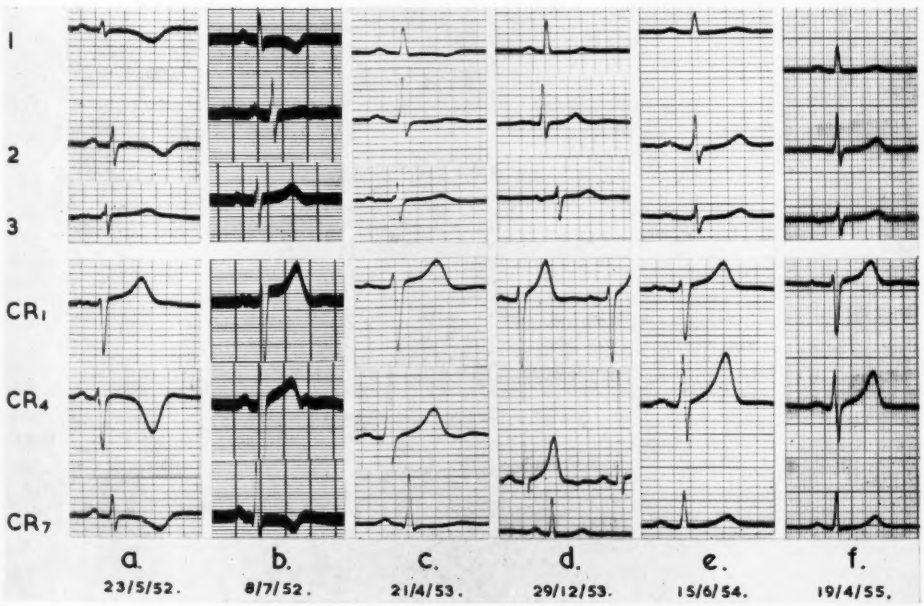

FIG. 1.—Case 1. (a). T wave inversion in I, II, CR4 and CR7 with iso-electric S–T segments. (b). T wave inversion in I and CR7 only with flat T2; the S–T segment shows 1mm. depression in I and CR7 ascribed to hypertension. (c), (d), (e) and (f). Stages in subsequent restitution of the graph.

The duration of the electrocardiographic changes varied considerably, as did the length of time necessary for complete recovery to occur. Fig. 1 shows T wave inversion persisting in CR7 for five weeks, and in lead I for at least a year before a change in direction occurred. In Fig. 2 there was a three-week interval between the recording of *a* and *c*, but these tracings are almost identical and no improvement is evident. Unless daily tracings are taken it is impossible to determine when improvement begins, and such an undertaking is frequently impracticable. It seems, however, that once improvement begins, it proceeds quickly and is unaffected by the length of time during which the tracing has remained abnormal. This rapid recovery, once initiated, is well illustrated by Case 5. Electrocardiograms taken on April 29 and May 14, 1953, are reproduced in Fig. 2. They are

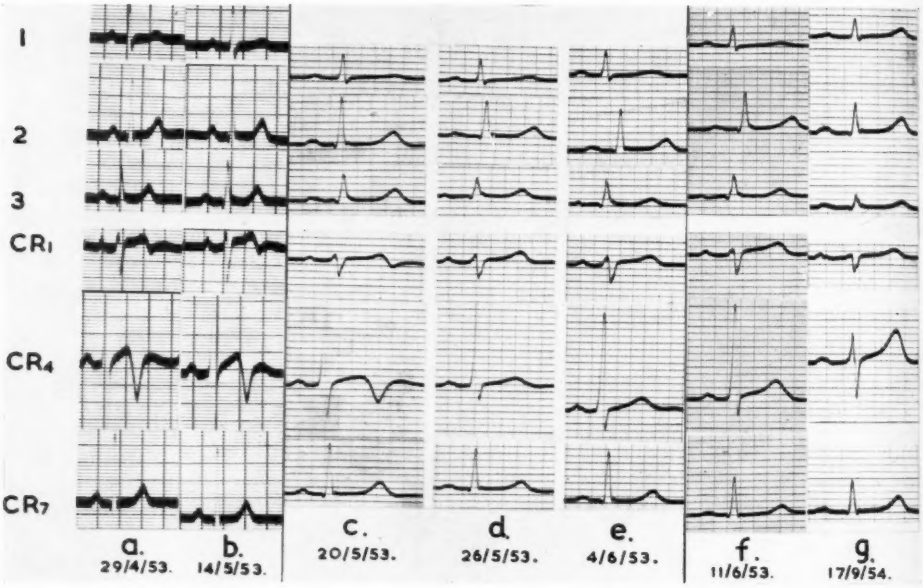

FIG. 2.—Case 5. (a), (b) and (c). Identical abnormailty in the T wave in CR1 and CR4. (d). Considerable improvement after one week in hospital, and further recovery is shown in (e) which is considered a normal tracing. This illustrates the rapid change in the direction of the T wave in CR1 and CR4 once recovery has been initiated.

identical, revealing gross T wave changes in CR1 and CR4. The patient was then admitted to hospital and the subsequent behaviour of the electrocardiogram is shown. On May 20 the T wave inversion was unchanged, yet six days later a remarkable improvement had taken place. Further improvement in the T wave in lead I and CR4 was evident over the next two weeks (Fig. 2 e and f).

It is extremely difficult to judge when complete reversion to the normal tracing has occurred, or when further improvement can be anticipated. Once an inverted T wave has become upright, an increase in its height is the sole indication that further recovery of the electrocardiogram has taken place. Opinions as to what constitutes a normal electrocardiogram in any individual vary widely, and argument has particularly centred around the height of the T wave in certain leads. Quite apart from any differences in the standardization of the tracings, this segment is peculiarly susceptible to changes in heart rate, posture, and body build and, in the case of the præcordial electrocardiogram, minor alterations in the position of the exploring electrode may exert a considerable influence. It is not therefore surprising that in the present series of patients, apparent improvement in the

electrocardiogram was sometimes observed even after it had been considered to have returned to normal. This particular point is well shown in Fig. 1.

In summary, it may be said that these electrocardiograms show a consistent pattern. Experience shows that when this pattern is seen, considerable and probably complete recovery of the electrocardiogram may be confidently predicted. The gross changes may persist for weeks without any prejudice to future recovery. When this recovery does begin, it may be very rapid to start with, remarkable improvement occurring within the space of a few days. Subsequent progress is usually slower and minor blemishes may evidently persist for months or even years.

The significance of this electrocardiographic pattern, in terms of underlying cardiac disease, is best discussed with the post-mortem findings.

Morbid Anatomy

Of the two patients who died, one (Case 4) had been observed for three months. His electrocardiograms are reproduced in Fig. 3; shortly after the last tracing in the series was taken he was admitted to another hospital where he died two weeks later. An electrocardiogram was recorded five days before he died; this is not illustrated here, but showed no change from Fig. 3d.

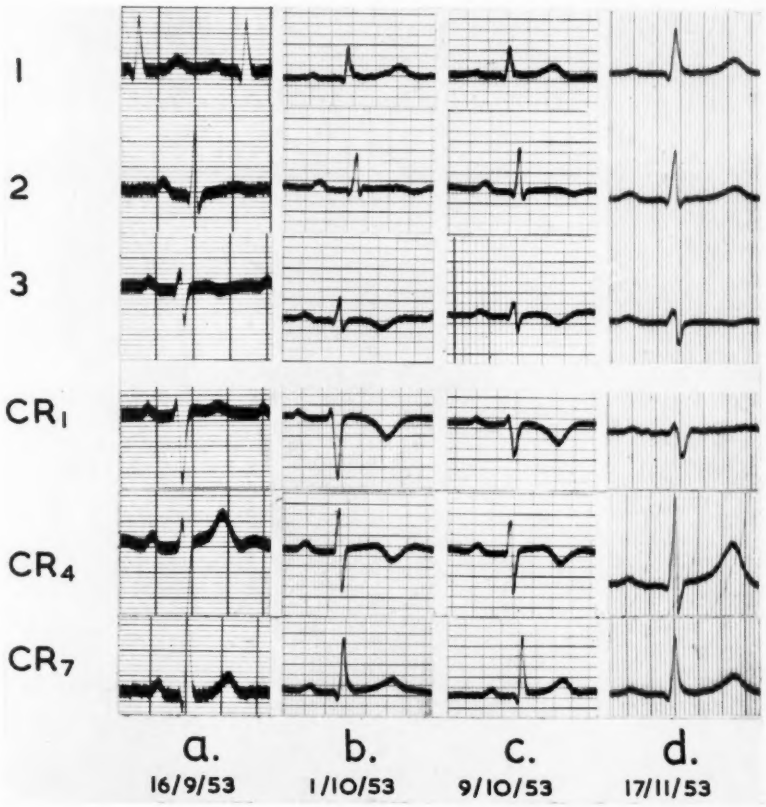

Fig. 3.—Case 4. (a). Taken on first attendance, shows flat T2 but otherwise normal tracing. (b) and (c) Characteristic T wave inversion. In (d) the only possible abnormality is flat T in CR1. (Death occurred three weeks later.)

Necropsy showed that death was due to recent massive embolism of the pulmonary trunk and both its main branches; there was evidence also of previous pulmonary embolism. The source of these emboli was shown to be the veins of the lower extremities, and the left femoral and iliac veins contained ante-mortem thrombi.

The heart weighed 344 g. and was not hypertrophied. A small infarct was found in the upper part of the interventricular septum. Macroscopically this infarct was certainly not very recent, but probably at least a month old. Unfortunately no sections were taken from the infarcted area, so that there is no histological evidence of the age of the infarct. There was severe generalized atheroma of both coronary arteries, and the anterior descending branch was particularly severely affected. Several areas of calcification and narrowing were seen, but no actual occlusions of a coronary artery or branch were apparent.

The second patient (Case 5, J. H.) died after twenty-two months of close observation and the electrocardiograms in Fig. 2 were recorded over this period. Necropsy was performed at the London Hospital. The immediate cause of death was infarction of the bowel due to atheromatous occlusion of the superior mesenteric artery at its origin. The heart was removed intact; it weighed 305 g. and was not hypertrophied. The coronary arteries were injected with radio-opaque mass using a modification of the technique described by Schlesinger (1938). The heart was then X-rayed with the results shown in Fig. 4. It is realized that there are theoretical objections to this technique as a means of judging the integrity of the coronary arteries. However, in practice the results appear trustworthy, and in the present case the coronary circulation seemed healthy and there was no evidence of any abnormality in the coronary system.

Subsequent examination confirmed this, for although atheroma was unusually severe and widespread throughout the body, the coronary arteries had been spared in a remarkable fashion and were described as " virtually free of atheroma ".

There were two or three bluish-white streaks about 1 cm. long in the posterior wall of the left ventricle

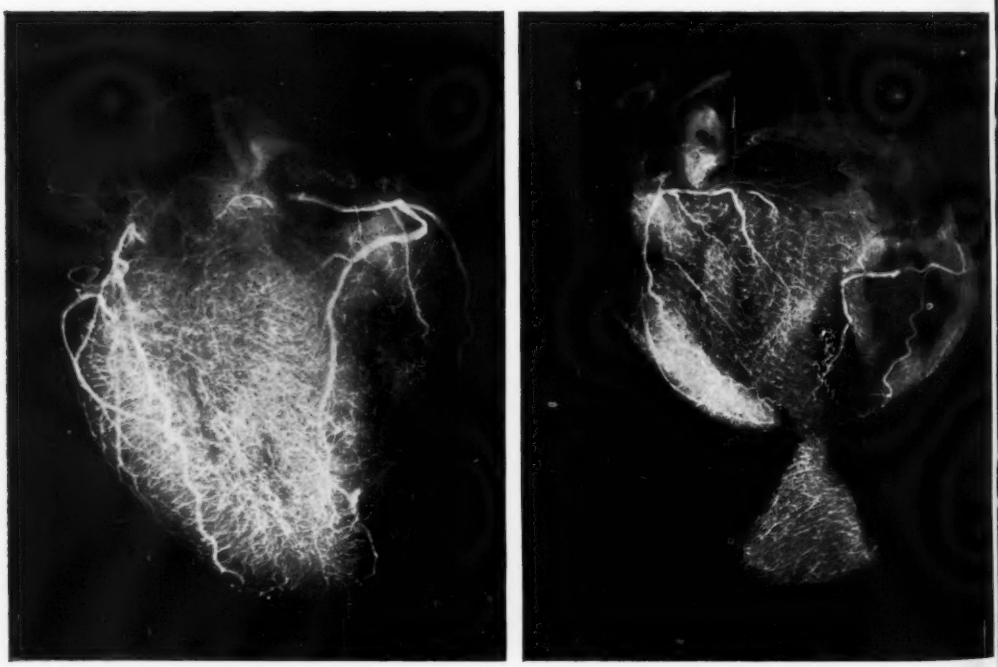

FIG. 4.—Case 5. X-ray photographs of the heart injected with radio-opaque mass. No obvious block is demonstrated in the coronary circulation.

near the apex, which extended into the interventricular septum. Apart from these, no macroscopic abnormality was detected in the heart. A photomicrograph from a section of the affected area is shown in Fig. 5.

A full histological report by Professor Dorothy Russell is given below.

"A section of the posterior wall of the left ventricle at the junction with the interventricular septum and right ventricle. The myocardium is occupied by fibrosis extending over an area measuring 1·5 cm. The fibrosis is reticulated to include irregular groups of muscle-fibres, many of which are hypertrophied. The collagen of the fibrosis is dense, and evidently of considerable age. There is no evidence of inflammation nor of progression of the fibrosis. None of the regional arteries suggests previous occlusion. The remainder of the myocardium appears healthy, apart from the presence of lipo-fuchsin granules in the cytoplasm of the fibres. The changes found, therefore, are indistinguishable from those of an old infarct."

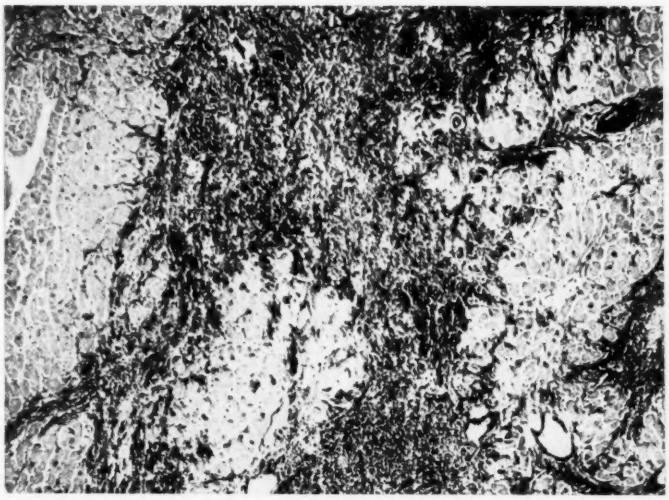

FIG. 5.—Case 5. Photomicrograph (× 62) of the area of fibrosis found at autopsy. Remnants of the injection "mass" can be seen in the arterioles which otherwise appear normal.

DISCUSSION

Evidence of cardiac infarction was thus found at necropsy in both fatal cases. The close similarity of the electrocardiograms, not only in the initial abnormalities but also in their subsequent behaviour, makes it probable that cardiac infarction had also occurred in the three patients who still survive. Accordingly this assumption will form the basis of the discussion that follows.

It has been mentioned that previous authors ascribed this type of electrocardiographic pattern to myocardial ischæmia. This is not in keeping with the usual description of the "ischæmic" tracing, the most important and consistent characteristic of which is depression of the S–T segment. Furthermore the diagnosis of cardiac ischæmia by the effort test frequently depends entirely upon the production of this feature. Yet in the present series significant S–T segment depression never occurred—an apparent discrepancy that requires explanation.

The term "ischæmia" implies that a living tissue is receiving an inadequate blood supply which is detrimental to the metabolism and function of that tissue. In the case of the heart, the clinical manifestation of this is ischæmic pain in the chest, or angina pectoris. Dead tissue cannot properly be considered to be ischæmic, since it performs no function and requires no supply of blood. Hence an electrode placed over an area of dead muscle will show changes of infarction and not of ischæmia.

Accepting, therefore, that cardiac infarction occurred in all the present series, there is no reason to postulate the presence of ischæmia and the apparent anomaly of the iso-electric S–T segment vanishes.

It is known that the production of a pathological Q wave depends upon the extent of muscle necrosis and hence upon the size of the area of infarction. Both infarcts revealed at autopsy were small and it is not surprising that they were not large enough to cause pathological Q waves. That they were in the interventricular septum in both instances fitted well with the electrocardiographic signs, for it was the præcordial leads, taken from the region of the septum, that showed the most consistent and striking changes. The extent to which these small infarcts encroach upon the anterior or posterior surfaces of the ventricle is presumably the factor that determines which particular limb lead will show T wave changes, when these occur.

There remains the question of the return to normal of the electrocardiograms. Remarkably little has been written on this important subject and most standard works on the heart do not even consider the possibility of such complete recovery after cardiac infarction. A possible explanation is that anastomotic channels develop which restrict the spread of the infarct, limit its extent, and allow the process of fibrosis and contraction of the scar to proceed unimpeded. Blumgart *et al.* (1940) demonstrated the existence of inter-coronary anastomoses, and Laubry *et al.* (1948) showed that the interventricular septum was rich in these anastomoses, which were particularly large and numerous after cardiac infarction. These findings were corroborated by Zoll *et al.* (1952). It would thus seem that circumstances are peculiarly favourable for the healing of small septal infarcts and for electrocardiographic recovery.

It has been shown that these electrocardiographic changes, which signify septal infarction, may persist for several weeks unchanged and subsequently improve quite quickly. Whether this static period of a month or so represents the time necessary for anastomotic channels in the septum to develop is unknown.

Although myocardial infarction usually results from coronary occlusion, it has long been recognized that post-mortem examination may demonstrate obvious cardiac infarction, yet fail to show any occlusion of the coronary arteries. Friedberg and Horn (1939) reported thirty-seven such cases and their findings were supported by Ravin and Geever (1946). Wang *et al.* (1948) were unable to demonstrate coronary occlusion in 39 per cent of all cases of myocardial infarction found at necropsy in a twenty-year period at the Massachusetts General Hospital. All these authors emphasized that in most instances severe disease of the coronary arteries was present with areas of coronary narrowing, and postulated that infarction of the heart resulted from prolonged anoxæmia as the result of inadequate coronary circulation. It was further suggested that hypertrophy of the myocardium from any cause, particularly systemic hypertension, would exaggerate the relative poverty of the coronary circulation so that any sudden " stress " such as exertion, tachycardia, humoral factors, or severe anæmia, might be sufficient to cause acute myocardial damage, although the coronary arteries remained patent. The corresponding clinical syndrome was termed " coronary insufficiency " by Master (1946) and " coronary failure " by Freedberg *et al.* (1948).

Of the two autopsies discussed in this paper, the first (Case 4) can evidently be placed in this category; no obvious coronary occlusion was found, but the coronary arteries were extensively diseased and a small myocardial infarct was seen. In the second autopsy (Case 5) cardiac infarction was associated with apparently normal coronary arteries. Although such findings are rare, they are by no means unknown; thus Lisa and Ring (1932) found normal coronary arteries at autopsy in seven instances in a series of one hundred myocardial infarctions, and Gross and Sternberg (1939) further reported fifteen examples of extensive myocardial infarction without significant disease of the coronary arteries. It is in such cases that the possibility of coronary arteriospasm merits serious consideration, for the absence of structural changes in the coronary vessels at necropsy leaves no satisfactory alternative explanation for myocardial infarction.

For many years clinicians have suggested that stimuli originating outside the heart might cause reflex spasm of the coronary arteries resulting in myocardial ischæmia, angina pectoris, and even cardiac infarction. In many earlier studies reported the gall bladder, stomach, and colon have been

the principal organs incriminated. Most of the evidence adduced to support this theory rests on the similarity in the type and distribution of the pain experienced by individual patients. It has been reported that changes in the electrocardiogram indicative of myocardial disease may disappear following the removal of gall stones (Fitzhugh and Wolferth, 1935; Miller 1942; Clarke, 1945). Most experienced physicians have witnessed the abolition of apparent angina pectoris in isolated cases by cholecystectomy. The association of hiatus hernia with chest pain and even electrocardiographic changes is well known, whilst the difficulty of distinguishing certain types of " heart burn " from cardiac pain needs no emphasis. Dworken *et al.* (1952) have recently shown that distension of the splenic flexure with a balloon in susceptible patients may cause substernal pain " very like " angina pectoris. In all these extra-cardiac syndromes it is frequently impossible to exclude the co-existence of coronary artery disease.

Of the present series of patients, three suffered from demonstrable organic disease in the digestive tract in addition to cardiac infarction; however, there is no objective evidence that this was other than a casual relationship. In one instance (Case 3) infarction occurred after cholecystectomy; in another (Case 5) the electrocardiogram remained normal at the time when his peptic ulcer symptoms were most severe, and thus presumably when reflex coronary arteriospasm might be expected. Although the occurrence of cardiac infarction in this patient remains unexplained, there is no direct evidence that reflex arteriospasm played any part.

It has been stated that the prognosis in patients presenting this reversible electrocardiographic pattern is good. East and Oram (1948) remarked that opportunities for necropsy were few and that the only post-mortem examination of their series revealed not heart disease but an obscure septicæmia; two areas of fibrosis were found in the anterior wall of the left ventricle near the apex, but the coronary arteries were stated to be perfectly healthy: these findings are very similar to those in the second necropsy reported in this paper (Case 5). Evans (1955) had no deaths in his series. Holzman (1955), who described similar electrocardiograms under the heading of " rudimentary anterior wall infarction ", wrote that " due to the good prognosis of the syndrome, personal post-mortem findings are lacking ". Obviously this universal paucity of pathological evidence has been a major factor in delaying the recognition of permanent structural cardiac damage in these cases and serves to emphasize that this damage is slight.

The state of the coronary arteries must, however, influence the prognosis. Although heart disease was not the direct cause of death in either of the two fatal cases in this series, in one (Case 4) severe coronary artery disease was found. The fact that most authors report a good prognosis indicates that this must be unusual. Nevertheless it would be of value if evidence of coronary artery disease could be obtained during life. Once the electrocardiogram has become normal the only objective means of assessing the functional state of the coronary arteries is by carrying out an exercise test, recording the electrocardiograms before and after exertion. Experience with this test shows that it may yield valuable information, but it is well recognized that the procedure can be dangerous. For this reason one patient (Case 3), an elderly woman with hypertensive heart disease, was not subjected to the test; another (Case 4) died before the test could be performed, and a third (Case 5) was unable to cooperate owing to severe claudication.

Effort tests were performed on the two remaining patients; one test was positive (Case 1) and the other negative (Case 2). In neither instance was cardiac pain produced, although the exertion was severe. Both patients are alive, and it is inferred that functionally significant coronary artery disease exists in the first patient but not in the second. Prognosis must be guided by these findings.

The cases reported in this paper show that the electrocardiogram can return to normal after localized infarction of the interventricular septum has occurred. Information concerning the incidence of this type of case would be extremely valuable. Of the present series all were referred to the Medical Unit Out-Patient Clinic, one of six general medical " firms " in a hospital that also maintains a large cardiac department. They were all seen for the first time between May 1952 and March 1954—a span of twenty-two months. It would thus seem that this type of " restricted " infarction may not be particularly rare in non-specialized clinics and although the actual incidence is

impossible to assess, the fact that the symptoms may not immediately suggest heart disease lends support to this view and possibly explains why these patients were not referred to a cardiologist in the first instance.

Summary and Conclusions

Five patients are reported in whom chest pain was accompanied by an abnormal electrocardiogram of a distinctive pattern which always reverted to normal. The characteristics of this pattern are described, and it is suggested that the subsequent behaviour of the electrocardiogram may be predicted.

From the findings at necropsy in two patients who died, it is concluded that this electrocardiogram is the result of localized infarction of the interventricular septum. The subsequent recovery of the electrocardiogram is discussed and is believed to be due to the development of intercoronary anastomoses in the septum.

The prognosis in this group of patients is generally good, but depends upon the extent of coronary artery disease in the individual case. It is suggested that the effort electrocardiogram may give useful information in this respect.

Reasons are advanced for the belief that this " syndrome " may not be particularly uncommon in general medical practice.

All these patients were in the care of Professor Clifford Wilson; it is a pleasure to express my gratitude for his permission to study these patients, and for his encouragement and advice in the preparation of this paper. I wish to thank Professor Dorothy Russell for the histological report on Case 5 and Dr. C. Raeburn for the necropsy findings in Case 4. The majority of the electrocardiograms were recorded in the Cardiac Department, London Hospital, and are available for reproduction by courtesy of Dr. William Evans. My thanks are also due to Sir John Parkinson and Dr. William Evans for much helpful criticism.

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ELECTROCARDIOGRAPHIC CHANGES DURING PRESSURE BREATHING

BY

R. J. SHEPHARD

From the RAF Institute of Aviation Medicine, Farnborough, Hants

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It was recognized many years ago that the form of the electrocardiogram could be modified by a voluntary increase of breathing pressure, as during the Valsalva manœuvre (Kahn, 1909). During the early part of the second world war further studies were undertaken by German workers (Zettel and Fink, 1939; Müller, 1941), and it was found that it was altered even by the small fluctuations of breathing pressure associated with the wearing of a gas mask.

At the altitudes of interest to modern aviation physiology, quite high positive breathing pressures may be necessary for survival, and such pressures produce dramatic alterations (Howard *et al.*, 1953; R.C.A.F., 1954), including occasional abnormalities of rhythm, and a consistent change in the standard limb leads interpreted as clockwise rotation (Howard *et al.*, 1953) or more cautiously as right axis deviation (R.C.A.F., 1954). The alteration in electrical axis is of particular interest: it offers a new technique for analysing the theoretical background to certain features of the electrocardiogram, and may also provide objective evidence of the success with which various counter-pressure garments maintain normal anatomical relationships during pressure breathing.

The present paper reports some measurements of the manifest electrical axis made during pressure breathing (with and without trunk counter-pressure) and during venous occlusion. Findings are correlated with other circulatory and respiratory changes observed during pressure breathing. The concept of a clockwise rotation of the heart in the frontal plane is confirmed, and it is concluded the electrocardiogram may indicate at least the order of this change.

METHODS

Electrocardiographic Technique. Simultaneous recordings of the three principal leads were obtained in some observations, and in these it was possible to follow fluctuations in the electrical axis from beat to beat. In the remaining observations, single channel recording was used, tracings for different leads being obtained by repeating the pressure breathing after the elapse of a few minutes. The two methods gave closely similar results, although with the second method it was only possible to measure the mean axis over the course of one respiratory cycle.

The standard technique (Wood, 1950) has been used to calculate the momentary manifest electrical axis of the heart, the maximum upright QRS deflection being determined in leads I, II, III, and CV, which measures the potential of a point on the back (one inch to the left of the seventh thoracic vertebra) relative to Wilson's neutral electrode. Potential changes in the frontal plane have been displayed on a conventional triaxial reference system (Bayley, 1943). Approximate values for the horizontal plane have been calculated from the resultant of leads I and CV, and for the sagittal plane from the resultant of leads II . cos 30° and CV. It seems clear from the detailed analysis of Frank (1954) that any attempt to estimate rotation in the horizontal and sagittal planes will be an approximation, and the above method of calculation was adopted on the grounds of simplicity rather than theoretical accuracy.

Muscle action potentials showed a marked increase during the course of pressure breathing. Their effect was minimized by the use of an appropriate filter throughout the experiments, but despite this, the precision of potential measurements was somewhat reduced during pressure breathing.

Subjects and Pressure Breathing Equipment. The subjects were four healthy young men, aged 20–26.

All had considerable experience of pressure breathing. Observations were made with the subjects strapped in an "ejector seat". A pressure breathing helmet and in some instances counter-pressure garments were worn, the equipment being inflated from the compressed air supply via a constant-pressure demand regulator. The desired breathing pressure was attained within five seconds, and thereafter it showed only slight respiratory fluctuations (not more than 2–3 mm. Hg).

Changes of pulmonary blood volume during pressure breathing were estimated by a pressure-spirometer technique (Rahn *et al.*, 1951). In the present observations, a conventional Knipping spirometer was " pressurized " by placing it in one lock of a decompression chamber. The end-tidal expiratory position and the expiratory reserve were recorded during normal quiet respiration and when pressure breathing, as illustrated in Fig. 1. Providing that subjects were able to expire maximally to at least the same chest volume when pressurized, the difference between the change of *recorded* end-tidal position and the change of expiratory reserve is an expression of alterations in the pulmonary blood volume during pressure breathing.*

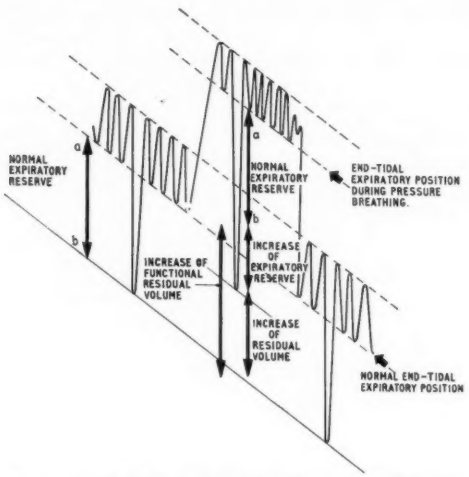

FIG. 1.—Alteration in pulmonary blood volume during pressure breathing. The amount is indicated by the difference between change of recorded end-tidal expiratory position and change of expiratory reserve.

Venous Occlusion. Occluding cuffs around the thighs and arms were inflated to a pressure just below the diastolic level (80 mm. Hg). The blood loss produced is of the following order: with cuffs on thighs only, 375 ml. after 5 minutes and 600 ml. after 10 minutes occlusion; with cuffs on thighs and arms, 555 ml. after 5 minutes and 860 ml. after 10 minutes occlusion. According to the data of Glaser and McMichael (1940), approximately one-half of this volume is derived from the pulmonary vessels.

Radiographic Measurements. Measurements of the cardiac axis, long and broad diameters, have been made in the manner suggested by Roesler (1937).

RESULTS

The Normal Electrical Axis of the Heart. Recent statistical studies (Kossman, 1953) have emphasized the wide range of absolute values for the cardiac axis. In the present small series, the greatest variation occurred in the frontal (coronal) plane, although there were also considerable inter-subject differences in the horizontal and sagittal planes.

* Fowler *et al.*, 1951, claim to have proved the constancy of the expiratory chest position during pressure breathing; in fact, if account is taken of concomitant changes of residual volume, the expiratory volume is somewhat decreased. The method may therefore tend to under-estimate the change of blood volume. Inaccuracies could also arise from an alteration in the gas content of non-respiratory structures such as the œsophagus. However, with the fixed visor headpiece this seems unlikely to be an important source of error.

Subject	Frontal (coronal) plane*	Horizontal plane†	Sagittal plane*
R.J.S.	38·7°–57·7°	17·8°–44·2°	62·0°–74·8°
D.Pl.	16·3°–30·7°	27·8°–31·0°	51·6°–57·2°
M.B.	70·3°–74·3°	43·8°–50·4°	68·6°–70·4°
D.Py.	79·2°–96·3°		

* Degrees below horizontal plane. † Degrees from frontal plane.

However, in any one subject, the mean direction of the cardiac axis was remarkably constant from day to day. In most complexes the R wave of lead I occurred a few milli-seconds prior to the R wave of leads II and III—a discrepancy that was noted by the earliest workers in this field (see Fahr, 1912). Careful measurements in subject D.Py. showed the differences in timing to average 63±4 milli-seconds.

Normal quiet respiration produced a swing of 8–17° in the frontal plane (clockwise during inspiration); rotation in the horizontal and sagittal planes were less than half as great. Counter-pressure garments covering the entire trunk produced no significant change of electrical axis in the uninflated state. Garments covering the thorax produced only a small (3–4°) clockwise rotation in the frontal plane.

The Electrocardiogram during Pressure Breathing. All subjects showed a large clockwise rotation in the frontal plane. This developed quite rapidly, reaching a maximum value within 10–15 seconds. The rotation at 15 seconds showed some correlation with the breathing pressure (Fig. 2), but the relationship was not linear, little further rotation occurring at the higher breathing pressures. At these higher pressures, subjects found it increasingly difficult to prevent voluntary contraction of the thoracic muscles. Some rotation was also observed in the horizontal plane (backwards) and in the sagittal plane (clockwise).

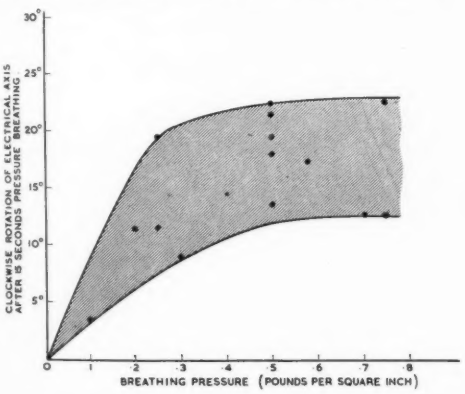

FIG. 2.—Rotation of the manifest electrical axis of the heart during pressure breathing (frontal plane). Four normal subjects.

Plane	Horizontal				Sagittal			
Breathing pressure (P.S.I.)	0·1	0·25	0·5	0·7	0·1	0·25	0·5	0·7
M.B.	−6·2°	−8·2°	−21·5°	−14·2°	+2·6°	+4·3°	+5·0°	+9·0°
D.Pl.	−0°	−0°	−0·5°	−7·0°		+7·9°	+10·5°	+10·1°
R.J.S.	–	−5·4°	−9·8°			+3·2°	+2·9°	

The range of respiratory fluctuations was somewhat smaller during pressure breathing, despite an increased scatter in the direction of the resultant potential (Fig. 3). This finding may readily be related to the reduced tidal volume that is typical of positive pressure breathing, particularly during its early phases (Rahn *et al.*, 1951; Shephard, 1956).

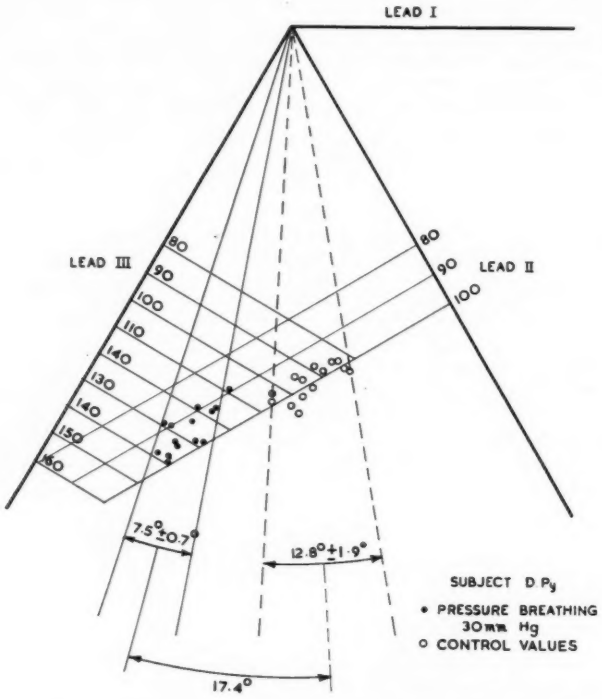

FIG. 3.—Triaxial reference system. To illustrate effect of pressurization on the electrical axis of the heart. There is a significant clockwise rotation (17·4°), scatter in the direction of the resultant potential is increased, and the respiratory fluctuations are significantly decreased.

Two other important cardiographic changes are an increase of the R wave lag, and an alteration in the pulse rate. The R wave phase change is small, but statistically significant. In D.Py. it amounted to 20±5 milli-seconds. Changes of pulse rate differed in sign from subject to subject, and cannot therefore have contributed to the changes of electrical axis. In R.J.S., the pulse rate decreased with pressure breathing, this change being greater at the lower breathing pressures. Subject M.B. also tended to a fall of pulse rate at the lower pressures, but above 0·3 P.S.I. (39 mm. Hg) there was a consistent rise of rate during pressure breathing. Subject D.Pl. showed an increase at all breathing pressures. Following release of the pressure, all subjects showed a sharp decrease of pulse rate that started within 2–3 seconds and reached a minimum after about 10 seconds—a minimum that was usually well below the normal resting level.

The Effect of Counter-pressure Garments. Rotational changes similar to those described above were noted, but a much higher breathing pressure was required to produce a given amount of rotation. The maximum effect was produced within 15–20 seconds, and if the pressure breathing

was continued, the shift of axis sometimes showed a slight decrease. Detailed results for a typical garment providing counterpressure over most of the trunk and lower limbs again suggest that frontal rotation reached a limiting value of 20–25°.

Subject	Frontal plane				Horizontal plane				Sagittal plane			
	26 (mm. Hg)	52	78	109	26	52	78	109	26	52	78	109
D.Pl.	+8·4°	+18·3°	+19·7°	+ 8·0°	+3·4°	+1·8°	−1·8°	+1·8°	+4·8°	+9·5°	+8·8°	+10·2°
R.J.S.	+8·5°	+15·0°	+24·5°	+21·9°	−3·4°	−8·6°			+2·0°	−0·8°		
D.Py.			+24·7°									

As in the experiments without chest counter-pressure, R.J.S. showed a consistent backward rotation in the horizontal plane, while in D.Pl. changes in this plane were small and variable. In the sagittal plane D.Pl. again showed a consistent clockwise rotation, while R.J.S. showed little change. A second type of counter-pressure garment (operating on the capstan principle) was also investigated in subject R.J.S.; rotation in the frontal plane was of a similar order (7·1° at 52 mm., 12·3° at 78 mm., and 17·1° at 99 mm. Hg).

With both forms of counter-pressure, respiratory fluctuations in the cardiac axis were rather less than at rest. The R wave phase lag was apparently slightly greater than in the experiments without counter-pressure, averaging 103±3 milli-seconds at a breathing pressure of 78 mm. Hg in subject D.Py. In all experiments, the pulse rate rose during the period of pressurization; the magnitude of this increase was related roughly to the applied pressure, subject R.J.S. showing a consistently greater response than D.Pl. Following release of pressure, the pulse rate decreased as in the experiments without counter-pressure, but the fall was less precipitous, and the minimum value was usually little below the normal resting value.

Changes of Pulmonary Blood Volume. Measurements by the pressure-spirometer technique suggest that changes of pulmonary blood volume amounted to 400–500 ml. when a subject was provided with trunk counter-pressure.

Subject	Breathing pressure	Changes in recorded end-tidal position	Change of expiratory reserve	Difference
R.J.S.	53 mm. Hg	773 ml. BTPS	395 ml. BTPS	378 ml.
R.J.S.	107 mm.	940 ml.	395 ml.	545 ml.

The volume of blood displaced seemed influenced to some extent by the state of the peripheral capacity vessels. If venous pooling in the lower limbs was restricted by the application of counter-pressure (using a standard anti-G suit), a correspondingly smaller change of functional residual volume was observed.

Subject	Breathing pressure	Change of F.R.V. without lower limb counter-pressure	Change of F.R.V. with lower limb counter-pressure	△	Calculated reduction in peripheral pooling*
R.J.S. ..	53 mm. Hg	933 ml. BTPS	773 ml. BTPS	160 ml.	165 ml.
D.Pl. ..	53 mm.	663 ml.	427 ml.	236 ml.	165 ml.

* This value has been calculated from the published pooling curves of Henry (1951) and Ernsting (1955), assuming that the lower limbs have a total volume of 20 litres, that counter-pressure is 75 per cent efficient, and that fluid filtration into the tissues has occurred for two minutes.

The Effect of Venesection on the Electrical Axis of the Heart. A functional venesection of this order, produced over the course of ten minutes by means of occluding cuffs, had little effect on the electrical axis of the heart. With cuffs on the thighs, the only significant change seemed a small anticlockwise rotation in the frontal plane.

Period of occlusion ..		1–2 min.	3–4 min.	5–6 min.	7–8 min.	9–10 min.
Frontal plane	R.J.S. ..	+1·4°	−0·1°	−1·9°	−1·1°	−1·0°
	D.Pl. ..	+1·5°	−2·2°	−3·7°	−4·4°	−4·5°
Horizontal plane	R.J.S. ..	−1·0°	+0·2°	+0·8°	+1·2°	+0·7°
	D.Pl. ..	−0·5°	−0·4°	+1·1°	+1·2°	+0·9°
Sagittal plane	R.J.S. ..	−0·1°	+0·7°	+0·8°	+1·3°	+0·6°
	D.Pl. ..	0°	−0·7°	+0·4°	+4·4°	−1·1°

With cuffs on both arms and thighs, a small clockwise rotation was observed, but even at the end of ten minutes it was in no way comparable with the changes observed during pressure breathing, being between 1° and 3° only.

Radiographic Changes during Pressure Breathing. Plates obtained before and after pressurization are illustrated in Fig. 4. The appearance is strikingly modified by pressurization. Measurement according to the method of Roesler (1937) shows the following changes when the garments were inflated to a pressure of 78 mm. Hg.

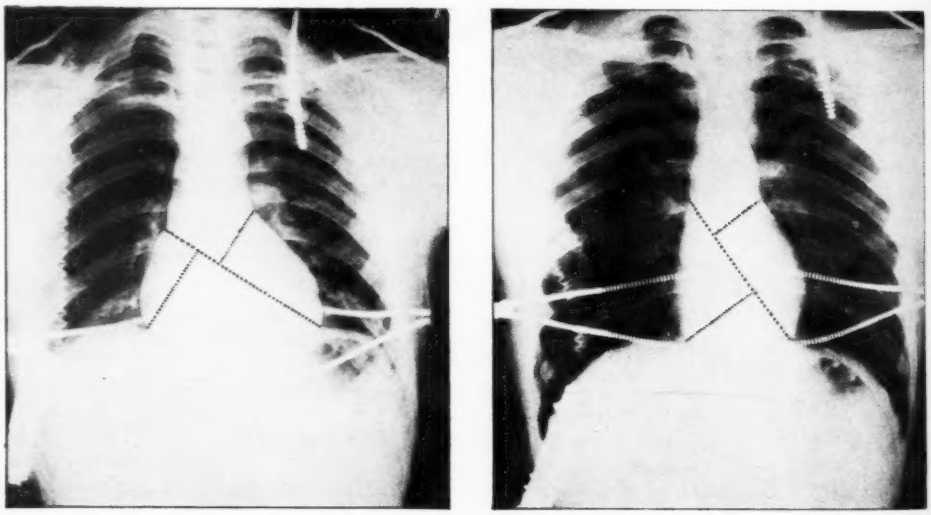

FIG. 4.—X-ray appearances before and after pressurization. Garment "A", inflated to pressure of 1·5 p.s.i. (78 mm. Hg). Long and broad diameters (Roesler, 1937) indicated by interrupted lines.

	Garment "A"	Garment "B"
Change of long diameter	−4·3%	−0·4%
Change of broad diameter	−7·5%	−7·4%
Rotation in frontal plane	22°	6°

It is difficult to measure changes of diaphragmatic level, owing to an increase in the angulation of the ribs, but it is clear that some descent occurs. In the region of the cardiac apex, it may be no more than 2–3 cm., but laterally it is much greater, as shown by the considerable decrease of the costo-phrenic angles.

Changes on Functional Residual Volume. In subject R.J.S., changes of electrical axis with two forms of counter-pressure garment were found to be closely similar. It was therefore of some interest to compare changes of functional residual volume, using these same two garments. Again, very similar values were observed: in garment A, a pressure of 53 mm. produced a change of 677 ml. (mean of 4 observations); in garment B, the change was 607 ml. at 27 mm., 773 ml. at 53 mm., and 940 ml. at 107 mm. Hg.

Discussion

It is now necessary to consider carefully how far the electrocardiographic changes noted above can be related to alterations in the anatomical axis of the heart.

Historical Evidence. The previous papers bearing on this problem have been concerned largely with absolute relationships between cardiographic and anatomical axes. Experimental conditions have often been rather remote from normal physiology, and while some authors have reported a close correspondence between the two axes, others have found considerable differences.

In the classical description of the method for determining the electrical axis (Einthoven *et al.*, 1913), it was recognized that the technique was empirical and that potential changes recorded from the extremities could be influenced by many variables, including respiration, heart rate (affecting mainly the P and T waves), stroke volume of the two ventricles, and the electrical conductivity of the tissues surrounding the heart. Other inherent fallacies noted in more recent years are the assumptions of (1) an infinitely small cardiac dipole and (2) a homogeneously conducting body torso with no differences of potential between right and left legs. Despite these theoretical limitations, Einthoven and his contemporary Groedel (1912) concluded that the method was satisfactory in practice, and gave a reasonable agreement with radiographic estimates of the anatomical axis. More recent investigations have included the following.

(1) Generation of dipole current in the heart of the cadaver (Fahr and Weber, 1914; Wagner, 1924; Wilson, 1934). Under these conditions, Einthoven's triangle gave an indication of the electrical axis that was correct to within 3–4°, except in the direction that fluid had accumulated.

(2) Generation of a dipole current in externally placed thoracic electrodes (Wilson *et al.*, 1949). This method showed a considerable discrepancy between the actual and calculated cardiac axes, but the results were largely invalidated by the abnormal position of the electrodes.

(3) Generation of a dipole current in the œsophagus (Abildskov *et al.*, 1951). This method suggested a fairly close relationship between the true axis and that calculated from Einthoven's triangle.

(4) Generation of a dipole current in a homogeneous, fluid-filled torso (Frank, 1954). In this system, quite large departures from the equilateral triangle concept were found. However, it was admitted that the body conductivity differed by as much as 15 per cent from a homogeneous torso, and the results are therefore of limited application to the human subject.

(5) Burger and Milaan (1946) have described an improved torso where some allowance is made for the relatively poor conductivity of the lungs and spine, but the model is still of necessity rather crude, and cannot fully represent the dynamic changes of conductivity occurring in the human. With their model, potential changes could be represented by a triangle, but it tended to be isosceles rather than equilateral in shape.

It seems fair to conclude from this survey, that the precision of the relationship between anatomical and electrical axis is still undecided, largely on account of experimental difficulties.

Specific Problems during Pressure Breathing. Certain specific difficulties attend the measurement of electrical axis during pressure breathing. Of these, the most important is a possible alteration

in the electrical conductivity of the viscera surrounding the heart. Einthoven *et al.* (1913) concluded that such changes did not contribute much to deviations of the electrical axis, since the magnitude of the resultant potential remained fairly constant. Katz and Korey (1935) and Lindner and Katz (1939) have challenged this conventional view. In a series of animal experiments, different aspects of the heart were insulated by a rubber diaphragm, and it was found that under these experimental conditions, a large part of the cardiac potential variations were conducted away from the posterior and inferior aspects of the heart, the air-containing portions of the lungs acting as insulators. Direct measurements of the specific resistance of the body have also shown that the trunk has a resistance about twice that of the limbs (Burger and Milaan, 1943), and this has again been attributed to the air content of the lungs. In the present study, the R wave phase change suggests that the conduction path to the lower limbs is disturbed during pressure breathing, probably by the altered blood content of the dependent parts of the lungs. On the other hand, this change of pulmonary blood content does not seem responsible for the alteration in electrical axis, since if a similar change is produced by venous occlusion (admittedly at a slower rate) no material change of axis is observed. It may therefore be concluded that displacement of blood from the pulmonary vessels does not influence the validity of the method used to determine the cardiac axis.

Correlation with Other Measurements. It is not possible to determine cardiac rotation with any precision from X-ray plates, but these do serve to confirm the view that there is cardiac rotation of the order suggested by the electrocardiogram. A second and rather more precise comparison is afforded by the correlation between changes of functional residual volume and changes of electrical axis. Again, a satisfactory correspondence is found, both measurements suggesting that in subject R.J.S. two different garments afford a similar amount of counter-pressure.

It may be objected that the descent of the diaphragm is insufficient to permit cardiac rotation, but a simple trigonometrical calculation shows that if the heart pivots about the mid-line of the body, a descent of 2–3 cm. in the region of the cardiac apex would be quite adequate to produce a rotation of 20°. Further, assuming the diaphragm to have an average area of 270 sq. cm. during quiet respiration, a descent of this order would increase the volume of the thorax by from 500 to 800 ml.—an amount that is quite compatible with direct measurements of this change. Descent of the diaphragm should be associated with a disturbance of the normal balance of pressures between pleural and peritoneal cavities, and there is some evidence that such a disturbance occurs during pressure breathing. While the pleural pressure follows the intra-pulmonary pressure to within 5–6 mm. Hg (Howard *et al.*, 1953; Roxburgh *et al.*, 1956), the intra-gastric pressure often lags as much as 10 mm. Hg behind the increase of breathing pressure (Parry, unpublished observations).

Thus the changes of electrical axis are in keeping with observations made by a number of independent methods, and it may be concluded that the electrocardiographic method indicates at least the order of anatomical rotation of the heart that occurs during pressure breathing.

Significance of Cardiac Rotation. As has been noted, rotation is governed largely by the extent of diaphragmatic descent, and in the relaxed subject shift of the electrical axis is therefore one further measure of the efficiency of counter-pressure (particularly abdominal counter-pressure). However, it is less satisfactory than more direct methods of measurement, since a small diaphragmatic movement can initially produce considerable rotation, but further descent produces progressively less effect. It seems probable that the limiting value of 20°–25° rotation is due largely to this consideration, although one cannot exclude the possibility that the limit of diaphragmatic movement has been reached. There is no evidence to suggest that cardiac rotation of this order has any adverse effect on circulatory function, and indeed in the recorded cases of misadventure during pressure breathing, death has usually been secondary to pulmonary damage.

Changes of Thoracic Blood Content. Changes in the blood content of the heart and lungs also merit brief discussion. All previous measurements seem to have been made without trunk counter-pressure. Methods have included the titre-board (Fenn *et al.*, 1951), changes in the vital capacity following a Valsalva manœuvre (Bahnson, 1951) and measurements of the residual air (Fowler

et al., 1951). These studies (mainly in the supine position) have shown that the volume of blood displaced is roughly proportional to the breathing pressure, a maximum of about 500 ml. being expressed within a few seconds at a breathing pressure of 30 mm. Hg. Even allowing for differences between the sitting and supine positions, the present study suggests that a higher pressure is necessary to displace a given volume if trunk counter-pressure is provided, and that this difference is even more pronounced if counter-pressure is provided over the lower limbs.

The heart makes a significant contribution to the total alteration of thoracic blood content during pressure breathing. Referring to measurements of the cardiac silhouette, the decrease of broad diameter is considerably greater than the change of long diameter. This is because the broad diameter is decreased by concurrent backward rotation, while the long diameter is increased by clockwise rotation in the sagittal plane. The true change of diameter is somewhere between these two estimates—perhaps 6 per cent in garment A, and 4 per cent in garment B. From Roesler's figures (1937), the average cardiac diameter is 10–11 cm., giving a total volume for the heart mass of some 500 ml. Calculation shows that if the diameter of this mass is reduced by 5 per cent, then the total volume decreases by approximately 75 ml. and neglecting small changes of muscle volume, it must be presumed that the heart sustains a blood loss of this order during pressure breathing.

Summary

Positive pressure breathing produces a rotation of the manifest electrical axis of the heart. In the frontal plane, rotation occurs in a clockwise direction, reaching a limiting value of 20–25° with increase of pressure. For a given pressure, rotation is less if trunk counter-pressure is provided.

There is an associated displacement of up to 500 ml. of blood from the heart and lungs, varying in amount with the breathing pressure and efficiency of counter-pressure. However, this does not seem responsible for the change of electrical axis, since a comparable change of blood volume produced by venous occlusion has little effect on the electrocardiogram. The blood loss from the dependent parts of the lung appears to do no more than slow the conduction of potential changes to the lower limbs.

There is sufficient agreement between changes of electrical axis, radiographic appearances, abdomino/pleural pressure gradients, and direct measurements of changes in functional residual volume to suggest that the electrocardiograph is indicating at least the order of anatomical rotation of the heart during pressure breathing.

Cardiac rotation appears related to descent of the diaphragm (probably through a cosine function), and is to this extent a measure of the efficiency of abdominal counter-pressure during pressure breathing. There is no evidence that rotation of the order noted has any adverse functional effect.

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COMPLETE HEART BLOCK IN AN EXPERIENCED PILOT

BY

FRANCIS A. L. MATHEWSON* AND FRED H. HARVIE

From the R.C.A.F. Cardiovascular Research Laboratory, Department of Medicine, University of Manitoba, Winnipeg, Canada, and the Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, U.S.A.

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The purpose of this communication is to report the finding of complete heart block, probably of congenital origin, in an experienced pilot. A normal G tolerance, a normal response to both strenuous exercise and anoxia, together with a lack of referable symptoms while in the air indicated his capacity to perform flying duties efficiently within the limits to which he was exposed.

In 1945, an apparently healthy flying instructor, aged 23, was referred for special investigation because of bradycardia and an apical systolic murmur found at the time of his annual aircrew medical examination. Apart from admitting some recent lack of energy he had been in good health since entering the service. He was one of three normal children, born of healthy Canadian parents. He had been active in sport, and had fainted but once, following an injury. His tonsils and adenoids had been removed for nasal obstruction when he was 8 years old. He had not been subject to sore throats and there was no history suggestive of rheumatic fever. His mother first became aware of his slow pulse when he was 10 years old. In 1941, at the age of 19, he was passed medically fit for aircrew duties with the Royal Canadian Air Force. Before this, he had worked for a short period in an explosives factory, blending cordite.

Early in his airforce career, he was a member of an experimental group used in a study of the cardiovascular response to strenuous exercise. Because of his slow pulse and freedom from distress after exercise he was thought to possess better than average physical fitness. He had flown a total of 1850 hours, of which 350 hours were logged in the past twelve months. He had never blacked out, although his vision became dimmed on rare occasions when performing tight manœuvres. The heart rates documented during his four years of service varied from 46 to 56 beats a minute. No heart murmurs were reported.

Physical examination showed a healthy well-built young man—height 66 inches, weight 139 pounds, pulse rate 48 beats a minute, blood pressure 130/68 mm. Hg. There was a faint systolic murmur at the apex transmitted to the midline which was best heard in the left lateral position and varied with respiration. In the supine position, a pulmonary systolic murmur was also heard. The liver edge was just palpable. Physical examination was otherwise normal. Blood sedimentation rate 7 mm. (Westergren). The heart was normal in size and contour by X-ray. The electrocardiogram showed complete heart block and was substantially the same as one taken ten years later (Fig. 3). Because of the early age at which bradycardia was recognized, the relatively rapid ventricular rate (Campbell, 1943) and the absence of other cause, it was concluded that his heart block was probably of congenital origin.

Further cardiograms were recorded with the pilot in various positions, after exercise and following the subcutaneous injection of atropine sulphate, 1/50th of a grain. In no instance did the ventricular rate exceed 60 beats a minute while the atrial rate, 83 at rest, rose to 115 on exercising fifty minutes after the injection of atropine (Fig. 1A).

In 1945, the subject was exposed to a simulated altitude of 22,000 feet in a standard R.C.A.F.

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decompression chamber. Cardiograms were taken periodically throughout the experiment. An altitude of 19,000 feet was reached at +15 minutes at which time he became pale, broke into a sweat, and complained of feeling faint. The pulse was hardly detectable and very slow. Oxygen (100%) was given by mask and recovery was immediate. The mask was removed at +23

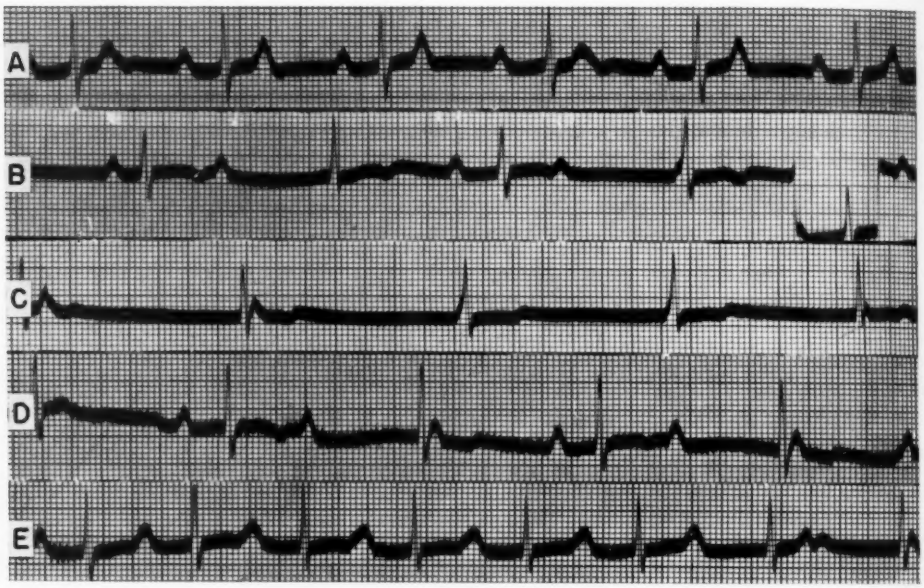

FIG. 1.—(A) Lead II. Following exercise, 50 minutes after the subcutaneous injection of atropine sulphate gr 1/50. Note apparent 2 : 1 relationship of atrial and ventricular complexes. The P wave following the QRS complex is superimposed upon the T wave.
(B) to (E) Lead II taken during decompression run:
(B) + 9 minutes. Before vaso-vagal attack.
(C) +16 minutes. During vaso-vagal attack.
(D) +18 minutes. After vaso-vagal attack. Breathing pure oxygen.
(E) +33 minutes. Atrial and ventricular rates are nearly identical. Each P wave is superimposed upon the preceding T wave.

minutes and an altitude of 22,000 was reached at +32 minutes. At +42½ minutes oxygen was administered again because of rapidly developing anoxia, by which time he had remained approximately 19 minutes at or above a simulated altitude of 19,000 feet. This was considered to be a normal response. Samples of lead II recorded before, during, and after the episode of near syncope are shown in Figure 1B, C, and D. Coincident with the attack there was an abrupt slowing of both the atrial and ventricular rhythms. This slowing taken in conjunction with the clinical picture suggests that the episode was of vaso-vagal origin. On reaching 22,000 feet (+32 minutes), the atrial and ventricular rates were both recorded at approximately 80 beats a minute (Fig. 1E).

On the afternoon of the same day the subject was placed in the human centrifuge and exposed to 2, 3, 4, and 4·5 G positive, each for a period of five seconds. The procedure followed was that developed by the accelerator section of the R.C.A.F. Institute of Aviation Medicine (Rose, 1942; Rose *et al.*, 1942; Kennedy *et al.*, 1943). In brief, a standard run is one in which the candidate is exposed for five seconds to a predetermined acceleration expressed in terms of the acceleration of gravity (G) at heart level. Thus a standard 3 G run is one in which the acceleration, applied for

five seconds at heart level, equals three times that of gravity. The total run requires 23 seconds to complete. An initial four-second period is required to reach 1·5 G, during the second 5 seconds the acceleration is built up to the predetermined G. This G is maintained for the next five seconds, following which five seconds are required to return to 1·5 G, and approximately four seconds more to bring the subject to rest.

The blackout threshold of the average healthy young pilot varies between 4 and 6 G with a range of 3 to 9 G. The normal pulse response is characteristic. Immediately preceding the run the pulse rate averages 95, the range being from 90 to 130 beats a minute. This tachycardia is thought to be emotional in origin. With the onset of acceleration there is an immediate and rapid increase in the heart rate which persists for 6 to 10 seconds after full G is attained and may thus persist for one to five seconds after the G has begun to decline. The maximum pulse rate varies between 120 to 196 beats a minute. Immediately following the run, the pulse slows usually to a level below that which was present before the run. This recovery phase is commonly characterized by one or more diminishing bursts of tachycardia.

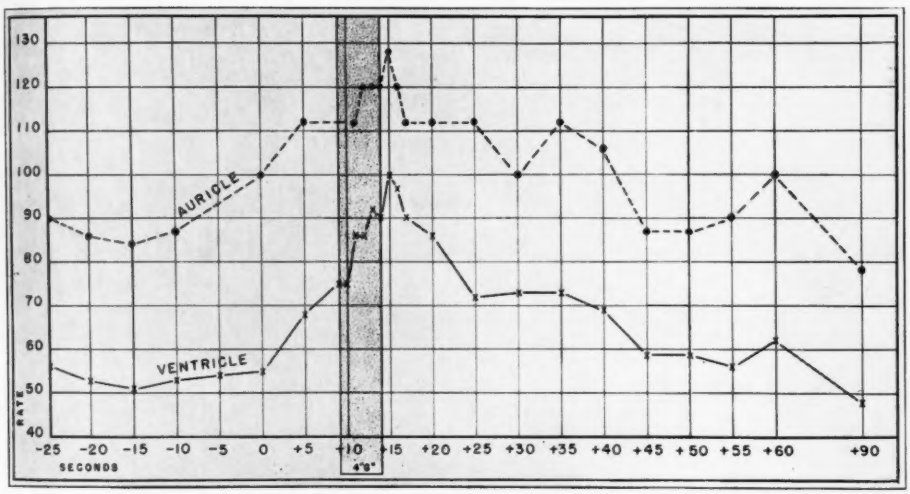

FIG. 2.—Response of auricular and ventricular pace makers to an acceleration of 4·5 G.

The present subject blacked out at 4½ G which is considered to be within the normal range of response. A continuous cardiogram showed that complete atrio-ventricular dissociation persisted throughout each run. The rates were calculated by measuring the distance between identical points on the three complexes (both atrial and ventricular) which most closely coincided with the moment of time being considered. The atrial and ventricular rates in response to the 4 G run are shown graphically in Fig. 2. The atria and ventricles responded in a similar manner, although their respective rates differed. The maximum atrial rate of 128 occurred one second following the five-second exposure to 4 G. It then fell off but was interrupted in the usual manner by secondary rises. The curve of the ventricular response was similar to that of the atria but at a slower rate. The maximum ventricular rate of 100 occurred at the same moment as the maximum auricular rate and the secondary rises were also coincident.

Because of freedom from subjective symptoms while flying, a normal response to anoxia and to positive G, and a failure to demonstrate any functional limitation, the pilot was returned to full flying duties. He continued to serve as a flying instructor until later that year, when at the age of 23 he was retired to civilian life with an unrestricted medical category.

He re-applied to the R.C.A.F. in 1950. In view of the favourable results of the 1945 investigation and the absence of abnormal findings on examination he was classified fit for full flying duties. Following a refresher course he was posted as an instructor to an elementary flying school and was serving in this capacity when seen by one of the authors in 1951. Apart from a short systolic

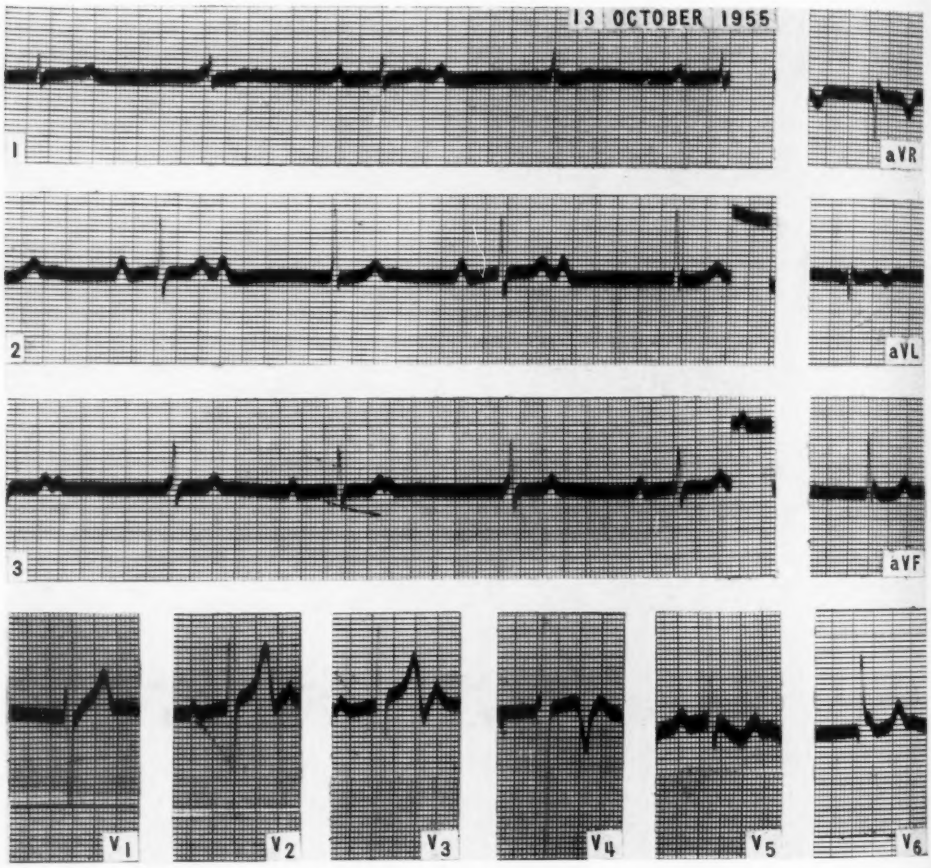

FIG. 3.—Electrocardiogram in 1955, showing complete A-V dissociation and abnormal T waves in V3–V5.

murmur at the apex, examination was normal. The cardiogram was unchanged from that recorded in 1945. He was now married and had two children: neither of them showed signs of heart disease and their electrocardiograms were normal.

In 1952, he converted to jet aircraft and flew as an examining officer at the R.C.A.F. Central Flying School, completing some 75 hours on jets and 375 hours on other single and multi-engine aircraft. His most recent flying achievement was to complete an advanced jet fighter course.

In October, 1955, he was referred for re-examination. By this time he had completed a total of 3000 flying hours and on no occasion had experienced symptoms while flying that could be attributed to an inefficient cardiovascular system. His personality was well integrated and he

exhibited a keen interest in flying. He admitted that recently his heart seemed to pound more than it used to do when he exerted himself.

On examination he weighed 142 pounds, his pulse was 48 beats a minute, and his blood pressure 132/78 mm. No heart murmurs were heard. The heart was of normal size and shape by X-ray. The cardiogram (Fig. 3) again showed complete heart block, and cardiograms with the subject in different positions and following exercise were recorded in a manner similar to those taken in 1945. The maximum atrial and ventricular rates were 88 and 75 respectively. These values were not exceeded following the intravenous injection of 1/30th of a grain of atropine sulphate.

While this pilot had an excellent flying record, he had reached the age of 33 years and was engaged in a type of flying that offered but little chance of survival should he even momentarily lose consciousness. It was ruled therefore that he be restricted to flying conventional aircraft.

Discussion

Throughout the period of observation all electrocardiograms showed complete heart block. On occasion, when the atrial rate was increased with (Fig. 1E) or without (Fig. 1A) a coincident increase in the ventricular rate the relationship of the atrial and ventricular complexes suggested that the impulse arising in the sinu-atrial node was conducted. An examination of those parts of the record that immediately precede and follow these particular sections shows clearly that the A-V association was apparent and not real. In response to certain specific stimuli the two rhythms reacted in a similar manner. An acceleration of both the atrial and ventricular rates occurred in response to anoxia and positive G. Marked slowing of both took place during the episode of near syncope which suggests that in addition to the S-A node the centre initiating ventricular activity was also subject to vagal inhibition. The ventricular complexes being of the supraventricular type this centre may well be located near the A-V node.

In the 1945 tracing the T wave in lead CF4 was inverted. Similarly in the 1955 tracing (Fig. 3) the T waves in leads V2–V5 were abnormal, although in V2 and 3 the second spike that follows the main T wave was atrial in origin. The reason for these T wave changes is not clear. How commonly they occur in congenital complete heart block is difficult to determine as illustrations in published case reports are selected to demonstrate changes in rhythm and seldom include præcordial leads. These were, however, normal in 6 of the 7 cases reported by Campbell and Thorne (1956).

Turner (1947) reported asymptomatic congenital complete heart block in a trained pilot which was identified after three years service, when he was referred because of bradycardia discovered during a routine physical examination. It was under similar circumstances that the present case was discovered. Campbell (1943) described a man with congenital complete heart block who was passed for flying duties with the Royal Air Force although he was not employed in this capacity.

Stokes-Adams attacks or paroxysmal tachycardia are uncommon in apparently healthy persons with congenital complete heart block (Campbell, 1943). On the other hand, Benjamin and White (1952) identified atrial flutter for the first time in a 55-year-old woman who had asymptomatic congenital complete heart block, and Jaleski and Morrison (1943) described a woman, aged 31, with congenital complete heart block who developed premature beats before delivery and who later under strain had fainting spells. Modern fighter aircraft are capable of reaching altitudes and accelerations that impose an exacting load upon the hæmodynamics of the pilot's cardiovascular system. While it is unlikely this pilot would develop an important disturbance in rhythm under these conditions, should such occur his chances of survival would be minimal.

Summary

A pilot, aged 33, with congenital complete heart block was followed for 10 years. He flew over 3000 hours in conventional and jet aircraft, including advanced operational flying. He experienced no adverse symptoms while in the air and showed a normal G tolerance and a normal response to

anoxia. Certain observations concerning the response of the atrial and ventricular pace makers are included.

The authors are greatly indebted to Prof. W. R. Franks for his critical review of the section pertaining to acceleration.

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PRÆCORDIAL BALLISTOCARDIOGRAPHY

BY

PATRICK MOUNSEY

From the Cardiac Department of the London Hospital

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Palpation of the heart beat has long been recognized to yield important information in heart disease. Many studies of graphic recording of the apex beat have been made (Marey, 1878; Mackenzie, 1902; Volhard, 1904; Weitz, 1917; and Dressler, 1937). More recently electronic methods have been used to record this movement (Johnston and Overy, 1951; Luisada and Magri, 1952). Recording of movement of the chest wall relative to a fixed point instead of to the surrounding chest wall was carried out by Eddleman *et al.* (1953), who used a metal bellows applied to the chest wall as a pick-up device.

In this investigation pulsation of the chest wall has been recorded by a new method, using an accelerometer. The accelerometer was kindly presented by Dr. Elliott. By means of this instrument it has been possible to record and study præcordial acceleration ballistocardiograms in health and disease.

The Investigation Described

The accelerometer described by Elliott *et al.* (1954) is an electrokinetic device that registers electrical effects produced at a mercury-sulphuric acid interface. It consists of a glass capillary tube containing alternate layers of metallic mercury and sulphuric acid, thereby creating multiple interfaces of mercury and electrolyte solution. Movement of the tube produces changes at the surfaces of the mercury and electrolyte solution and these in turn give rise to variations in electrical potential that are proportional to the rate of change of velocity imparted to the tube. The instrument is most sensitive to acceleration in its longitudinal axis and was found by Elliott *et al.* to be capable of a flat response from 0 to 3000 cycles per second. The theory of the mercury-sulphuric acid interface phenomenon or so-called " U effect " was given by Ueda *et al.* (1950 and 1951) and was further discussed by Yeager and Hovorka (1953) in a review of acousto-electrokinetic phenomena.

In the present investigation the instrument used was a metal tube shielding the glass capillary tube and mounted on a light wooden bar (Fig. 1). The instrument was strapped to the chest by two rubber bands in such a way as to respond to movement in an axis at right angles to the body surface. The areas selected for recording were the site of the apex beat or apical area, the upper sternal area at the level of the second intercostal space, and the lower sternal area at the level of the fourth intercostal space. The subject lay resting on a steady couch, which was covered with a firm mattress, with the upper part of the body raised to an angle of 45°. The output from the accelerometer was fed into the electrocardiograph amplifier of a Sanborn Twin-Viso recorder.

The apparatus was so arranged that acceleration of the chest wall in an outward direction produced a downward deflection in the record.

Standardization of 0·5 cm. per millivolt was adopted, being found to give a convenient sized tracing in most subjects. No exact quantitative estimation of acceleration due to the heart beat was attempted, since a number of extraneous factors influenced the voltage of the ballistocardiogram. These included the tightness of the rubber bands strapping the instrument to the chest, the amount of subcutaneous tissue, the build of the chest, and lastly the varying angle, that the long axis of the accelerometer tube subtended with the direction of gravity.

Twenty healthy subjects were studied. There were 14 men and 6 women and their ages varied

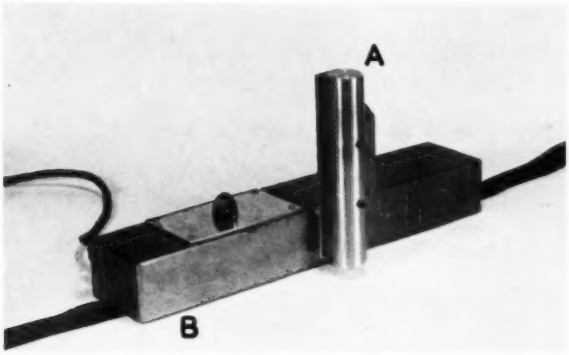

FIG. 1.—The accelerometer. The vertical metal tube (A) shields the glass capillary tube containing the mercury and sulphuric acid interfaces. The horizontal cross-piece (B) is a light wooden block which is strapped to the chest wall.

between 23 and 60 years. In addition, examples of some common heart diseases were investigated; these included seven patients with systemic hypertension, seven with pulmonary hypertension, three with atrial septal defect, three with constrictive pericarditis, twenty with mitral stenosis, three with dominant mitral incompetence, two with aortic stenosis, three with severe aortic incompetence, one with tricuspid stenosis, four with tricuspid incompetence, and six with left heart failure due to hypertension, cardiac infarction, or aortic incompetence.

As *reference tracings* a simultaneous electrocardiogram and a low-frequency phonocardiogram were recorded. In the study of the 20 healthy subjects a simultaneous low-frequency phonocardiogram was recorded in all, and both a phonocardiogram and an electrocardiogram in 12.

Interpretation of the Acceleration Ballistocardiogram. Acceleration bears no direct relationship to either displacement or velocity, although both may be derived from it mathematically. It is, however, closely related to motive force. Thus, in the ballistocardiogram the same deflection may mean either acceleration in one direction or deceleration in the opposite direction, but the direction of the motive force required to produce these changes in velocity would in either case be the same. Hence, although the direction of motion is not at once discernible from the record, the direction of motive force is clearly seen. In analysing the acceleration ballistocardiogram, therefore, the main deflections have been related as far as possible to the successive forces acting during the cardiac cycle.

THE PRÆCORDIAL BALLISTOCARDIOGRAM IN HEALTH

In the healthy subject the direction of the main deflections in the ballistocardiogram is similar, whether the recording is made at the apex, the upper sternal or lower sternal areas. The relative amplitude of the deflections, however, and also their exact timing differ according to the area selected for recording. In addition, in late systole and early diastole the direction of certain deflections is reversed in some patients in the upper sternal as compared with the apical area. In this paper the analysis of the ballistocardiogram in health will be confined to the study of records from the apical area, although brief mention will be made of the record in the upper sternal area, where this differs significantly from that in the apical area.

The præcordial ballistocardiogram may be conveniently divided into eight periods adopting a modification of the classification of Wiggers (1939) and Eddleman *et al.* (1953): atrial systole, ventricular proto-systole, ventricular isometric contraction, ventricular maximum ejection, ventricular reduced ejection, isometric relaxation, diastolic rapid inflow, and diastasis.

In *atrial systole* the ballistocardiogram showed an initial downward deflection AS^1 followed by an upward deflection AS^2 (Fig. 2 and 3). These deflections corresponded with forces generated

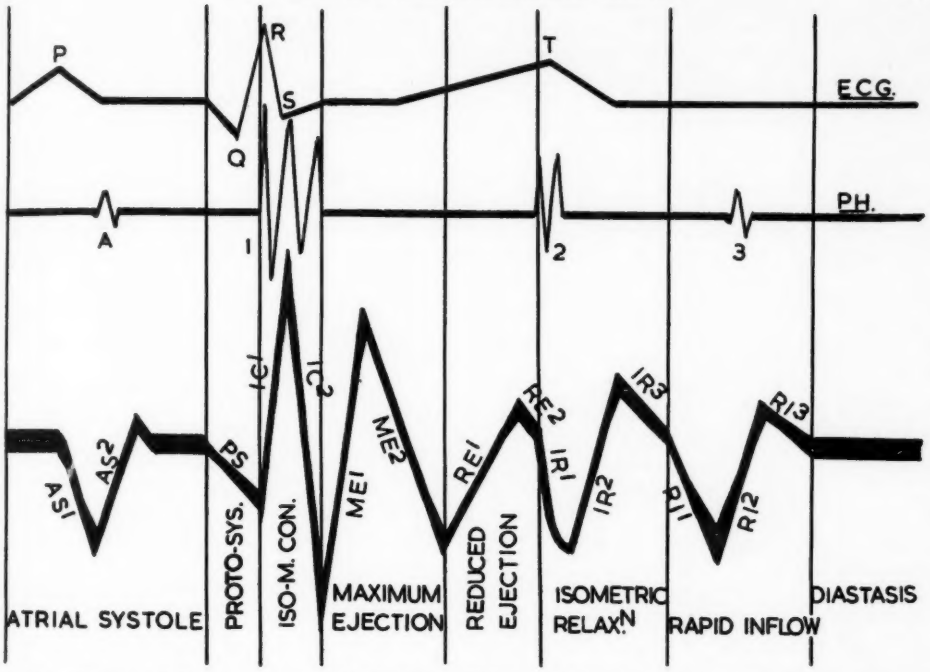

FIG. 2.—Diagram of the normal præcordial ballistocardiogram in the apical area. Simultaneous electrocardiogram and phonocardiogram as reference tracings. The præcordial ballistocardiogram is subdivided into eight periods: atrial systole, ventricular protosystole, ventricular isometric contraction, maximum ejection, reduced ejection, isometric relaxation, diastolic rapid inflow, and diastasis. The deflections in the ballistocardiogram bear two initials indicating the period in which they occur, followed by a number indicating their order of sequence: e.g. in the period of maximum ejection, the deflections are marked ME^1 and ME^2.

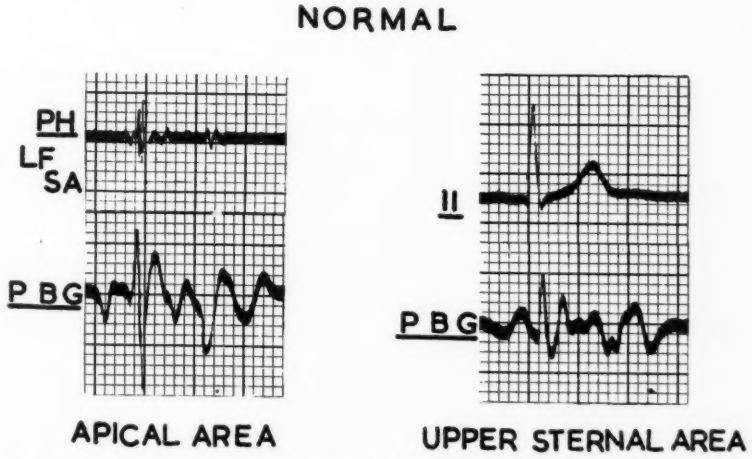

FIG. 3.—The normal præcordial ballistocardiogram in the apical and upper sternal areas.

by atrial contraction, causing initial outward acceleration followed by retardation in the second half of atrial systole. The average time interval between the beginning of the P wave in the electrocardiogram and the beginning of the atrial downward deflection in the ballistocardiogram was 0·08 sec. in the 12 subjects in whom a simultaneous electrocardiogram was recorded.

Ventricular proto-systole is here defined as the period between the beginning of the Q wave in the electrocardiogram and closure of the auriculo-ventricular valves, as indicated by the first heart sound in the phonocardiogram. In this period the initial deflection PS in the ballistocardiogram was downwards in seven of the twelve subjects. In the remaining five subjects it was preceded by a small upward deflection. The average time interval between the beginning of the Q wave in the electrocardiogram and the trough of the downward deflection PS in the ballistocardiogram was 0·05 sec., the mean heart rate for the twelve subjects being 85 a minute. The downward deflection PS and the inconstant upward deflection preceding it corresponded with forces due to ventricular contraction preceding closure of the auriculo-ventricular valves. The PS deflection was independent of atrial systole, since it was seen in the presence of atrial fibrillation.

In the ventricular isometric contraction period there was an abrupt upward deflection IC^1, which coincided with the first heart sound in the phonocardiogram. The average intervals between the Q wave in the electrocardiogram and the beginning and the peak of the upward deflection were 0·05 and 0·08 sec. respectively. The IC^1 deflection was thought to be due to inward directed forces resulting from closure of the auriculo-ventricular valves. The upward deflection was followed by a downward deflection IC^2. This deflection corresponded with a period of continued isometric contraction between closure of the auriculo-ventricular valves and opening of the semilunar valves and indicated outward-directed forces due to ventricular contraction.

In the period of maximum ventricular ejection the first deflection ME^1 was large and upward. The beginning of the deflection measured on an average 0·11 sec. from the Q wave in the electrocardiogram and its peak 0·15 sec. This deflection corresponded with inward-directed forces at the beginning of ventricular ejection into the aorta and pulmonary artery. The beginning of the deflection probably coincided with the opening of the semilunar valves and in a patient with pulmonary hypertension the ejection sound (Leatham and Vogelpoel, 1954) was seen to occur at this time (Fig. 4). The upward deflection was succeeded by a downward deflection ME^2: this deflection indicated a period of lessening acceleration of ejection following the initial period of increasing acceleration at the beginning of ventricular ejection.

The period of ventricular reduced ejection is here defined as beginning at the trough of the ME^2 deflection, which measured 0·23 sec. from the Q wave in the electrocardiogram. In this period an upward deflection RE^1 was seen in six out of twelve healthy subjects, while in the remaining six the tracing remained at the base-line throughout this period. Whether this inconstant deflection originated primarily from forces in the heart or the great vessels seemed uncertain. The RE^1 deflection was followed by an inconstant small downward deflection RE^2.

In the isometric relaxation period, in records from the apical area the initial deflection IR^1 was downwards and its beginning coincided with the sound of closure of the semilunar valves in the phonocardiogram. In records from the upper sternal area the direction of the IR^1 deflection was reversed, being upwards. This reversal in the two records could be explained by an inward force over the great vessels and a simultaneous outward force over the apex of the heart at the time of closure of the semilunar valves. Where splitting of the second heart sound was wide in the phonocardiogram the IR^1 deflection had a double trough. The average interval between the beginning of the second heart sound in the phonocardiogram and the trough of the IR^1 deflection was 0·03 sec.

A second deflection, IR^2, followed the IR^1 deflection. It was upward at the apical area, although reversed in sense at the upper sternal area. The average time interval between the second heart sound and the peak of the IR^2 deflection was 0·08 sec. This deflection appeared to indicate inward forces over the apex of the heart accompanied by outward forces over the base of the heart, during the period of ventricular relaxation prior to opening of the auriculo-ventricular valves. These forces may possibly be explained by the alteration of the general position of the heart during this

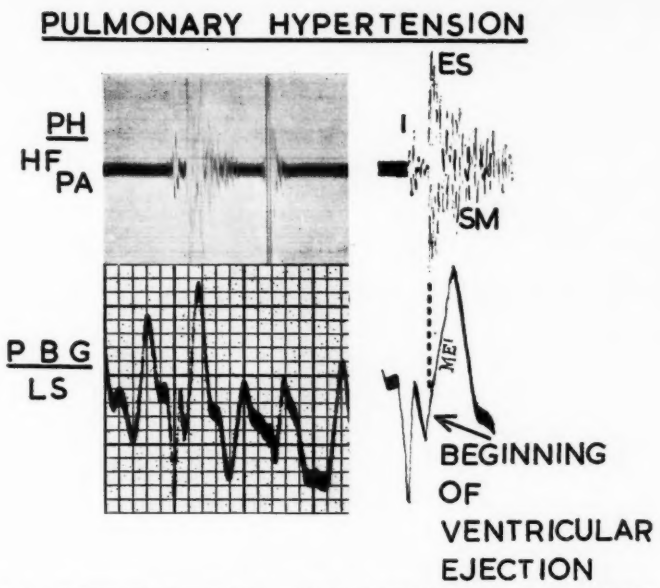

FIG. 4.—Pulmonary hypertension. Coincidence of the ejection sound (ES) with the start of ventricular ejection, as indicated by the beginning of the ME^1 deflection in the præcordial ballistocardiogram. ME^1 = first deflection in the maximum ejection period. SM = systolic murmur.

period. The IR^2 deflection was followed by a small downward deflection IR^3 of variable duration, which ended with the downward deflection of the rapid inflow period.

The period of diastolic rapid inflow is defined as beginning with a relatively sharp downward deflection RI^1 and ending with the return of the succeeding upward deflection RI^2 to the base-line. An inconstant small downward deflection RI^3 following the RI^2 deflection was sometimes seen. The onset of the downward deflection RI^1 averaged 0·13 sec., and its trough 0·16 sec. from the beginning of the second heart sound. The return to the base-line of the succeeding upstroke RI^2 averaged 0·23 sec. from the second heart sound.

The beginning of the downward deflection RI^1 probably coincided with the opening of the auriculo-ventricular valves and in mitral stenosis was found to be simultaneous with the opening snap (Fig. 9). The downward deflection RI^1 was due to the outward forces of early acceleration of ventricular filling. The succeeding upward deflection RI^2 was due to gradual lessening of acceleration of filling. A third heart sound was recorded in one young healthy subject and was seen to coincide with the upward deflection RI^2.

In *diastasis*, or the period of reduced filling, the tracing remained on the base-line and did not show any significant deflection. This flat tracing was compatible with slow even filling of the ventricle during this period.

THE PRÆCORDIAL BALLISTOCARDIOGRAM IN DISEASE

In order to assess the possible value of the ballistocardiogram as an ancillary diagnostic aid examples of some common heart diseases were investigated.

The *heaving apex beat* in a patient with left heart failure due to *systemic hypertension* was examined in the ballistocardiogram (Fig. 5). An abnormally large downward deflection was recorded in the

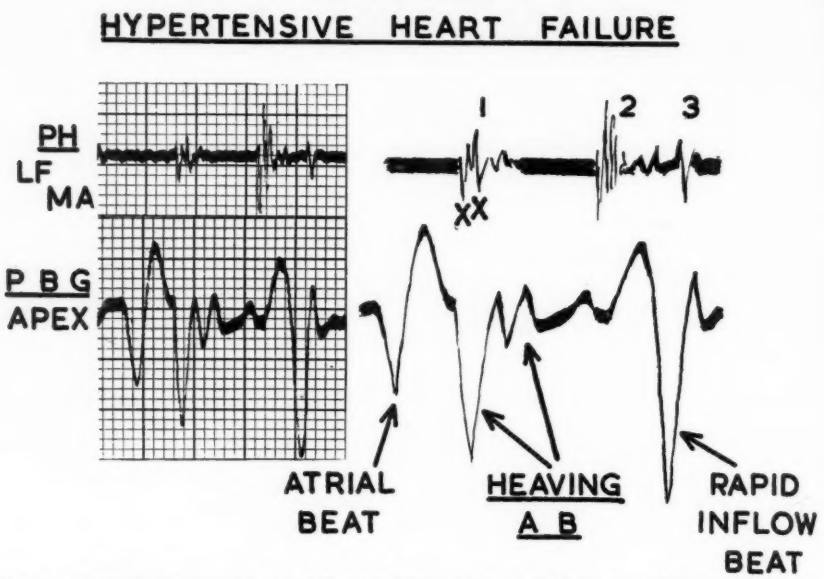

FIG. 5.—Systemic hypertension and left heart failure (B.P. = 250/140 mm. Hg). Heaving apex beat. Quadruple rhythm, due to the addition of atrial and diastolic rapid inflow beats. 1, xx = split first heart sound.

apical area during the beginning of ventricular systole, which was followed by a large, but only moderately abrupt, upward deflection. The first heart sound was split in the phonocardiogram and the upward deflection in the ballistocardiogram was seen to coincide with its second component, thought to be due to closure of the mitral valve which was delayed and followed closure of the tricuspid valve. The downward deflection in the ballistocardiogram indicated large outward forces at the beginning of ventricular systole, followed by large, but only moderately abrupt, inward forces at the time of closure of the mitral valve. The succeeding deflections during the period of ventricular ejection were not abnormally large. This abnormal series of forces and their smooth, as opposed to abrupt, succession reflected the heaving quality of the apex beat felt by the hand.

The *palpable quadruple rhythm* in the same patient with hypertensive heart failure was reflected in large deflections in the ballistocardiogram during the period of atrial systole and of diastolic rapid inflow. These deflections indicated outward forces of unusual magnitude, which formed the third and fourth components of palpable quadruple rhythm and coincided with the atrial and third heart sounds.

For comparison the ballistocardiogram of a second patient with systemic hypertension of the same order (250/140 mm. Hg) was studied. This patient had few symptoms, no triple rhythm, a normal-sized heart on screening, an electrocardiogram showing slight left ventricular preponderance only and a ballistocardiogram that appeared normal. In four other patients with systemic hypertension differing patterns of ballistocardiogram were seen, which mirrored the wide variation in character of the apex beat.

Examples of left ventricular enlargement due to aortic incompetence and stenosis have been studied. In a patient with free *aortic incompetence* there was an abnormally large downward deflection at the beginning of ventricular systole. This was followed by an abnormally large and abrupt upward deflection, which was thought to coincide with closure of the mitral valve which was delayed and followed closure of the tricuspid valve. This upward deflection was partly fused with the succeeding upward deflection in the period of maximum ejection (Fig. 6). These deflections

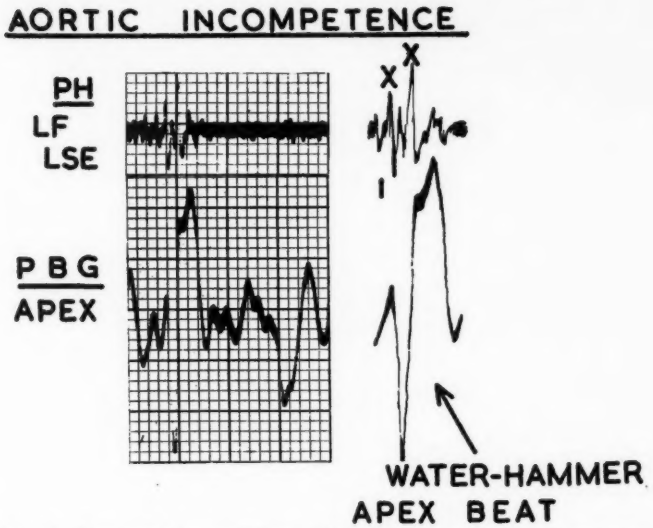

FIG. 6.—Free aortic incompetence. Water-hammer apex beat. 1, xx = split first heart sound.

indicated increased outward forces at the beginning of ventricular systole, followed by abnormally large and abrupt inward forces at the time of closure of the mitral valve and at the beginning of ventricular ejection, the latter reflecting the water-hammer quality of the pulse.

In *aortic stenosis* the abnormally large and abrupt fused upward deflections at the time of closure of the mitral valve and at the beginning of ventricular ejection were not seen in the patients studied.

In a patient with *atrial septal defect* and *pulmonary hypertension* the tapping beat and left parasternal lift were studied in the ballistocardiogram. The *tapping beat* was characterised by an abnormally large downward deflection during protosystole, followed by an abrupt and large upward deflection at the time of closure of the auriculo-ventricular valves. This deflection in turn was followed by a large upward deflection at the beginning of ventricular ejection, which was sometimes partially fused with the preceding upstroke (Fig. 7). These deflections indicated an initial outward force in protosystole, followed by abnormally abrupt and large inward forces both at the time of closure of the auriculo-ventricular valves and at the beginning of right ventricular ejection. This sequence of forces was appreciated by the hand as an abrupt tapping beat.

The left *parasternal lift* was characterized in the ballistocardiogram by an abnormally large upward deflection during the period of reduced ejection. The resultant M-shaped figure inscribed in the ballistocardiogram during the period of maximum and reduced ejection was found to be characteristic of this lifting movement of the præcordium.

In two patients with *acquired pulmonary hypertension* and no intracardiac shunt, in one due to pulmonary vein obstruction by granulation tissue and in the other to recurrent pulmonary embolism, the ballistocardiogram showed in general a normal pattern, although the amplitude of the deflections during the period of ventricular systole was increased in both and in one the atrial beat was greatly augmented. Apart from the palpable atrial beat neither patient showed clinically the characteristic pulsations associated with right ventricular hypertrophy.

The palpable triple rhythm of constrictive pericarditis was well demonstrated in the ballistocardiogram and this offered confirmatory evidence that abrupt halting of rapid ventricular filling was the cause of the added early diastolic sound (Mounsey, 1955). During the period of diastolic rapid inflow the initial downward deflection was abruptly terminated by a steep upstroke, which in turn was followed by a downward deflection with return to the base-line (Fig. 8). The diastolic sound in

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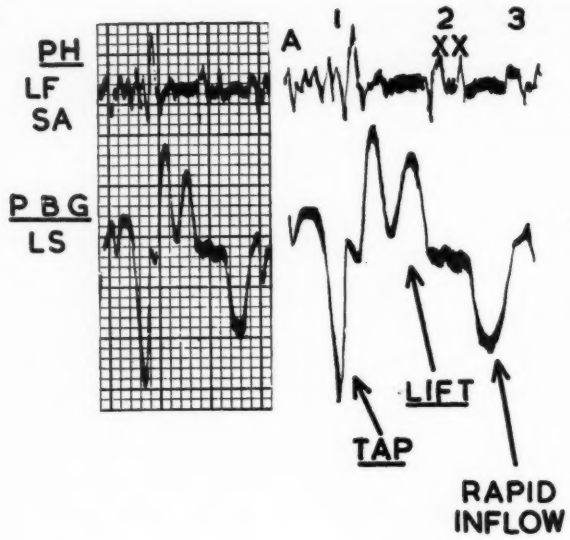

FIG. 7.—Atrial septal defect and pulmonary hypertension. Tapping beat and left parasternal lift. Large rapid inflow deflections. 2, xx = split second heart sound. At cardiac catheterization pulmonary artery pressure at 70/35 mm. Hg; evidence of left-to-right shunt in right atrium.

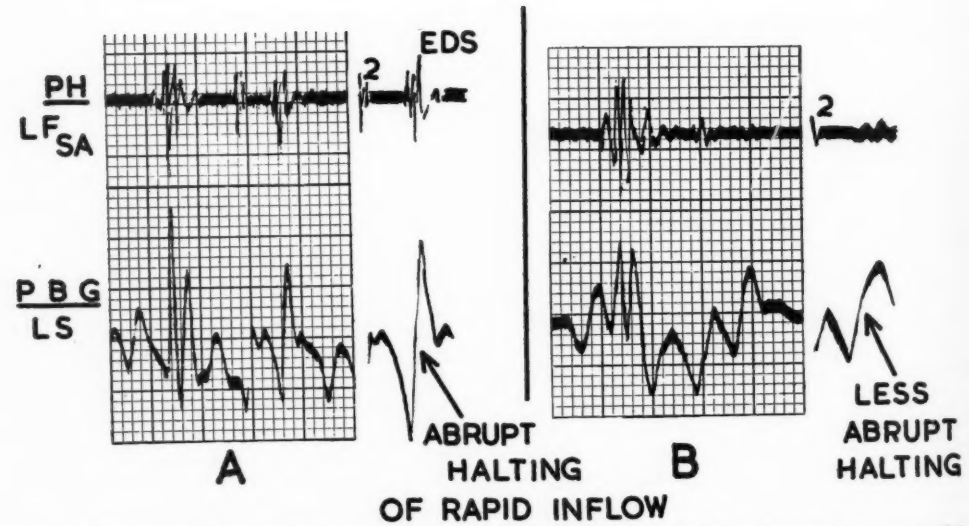

FIG. 8.—Constrictive pericarditis. Abruptness of halting of rapid ventricular filling decreased after successful operation. A = before operation. B = the same patient after operation. EDS = early diastolic sound.

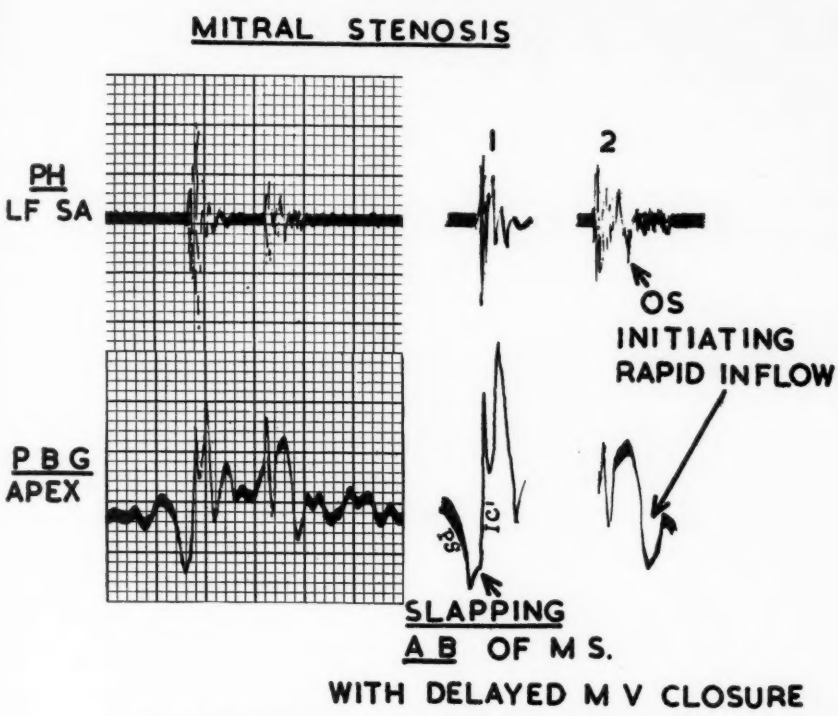

FIG. 9.—Tight mitral stenosis and atrial fibrillation. Slapping apex beat with delayed mitral valve closure, which coincides with the IC^1 deflection in the præcordial ballistocardiogram. Opening snap (OS) initiating premature and abbreviated diastolic rapid inflow period. PS = protosystolic deflection. IC^1 = first deflection in the isometric contraction period.

the phonocardiogram was seen to coincide with the steep upstroke in the ballistocardiogram. The initial downward deflection indicated outward forces due to rapid ventricular filling, as a result of the high venous pressure. The steep upstroke indicated abrupt halting of the outward forces of ventricular filling, which results from constriction of the expanding ventricle by the rigid pericardial casing. After successful operation the ballistocardiogram remained abnormal, although the steepness of the upstroke in the period of diastolic rapid inflow diminished, indicating that halting of ventricular filling was less abrupt.

In *mitral stenosis* the delay in mitral valve closure and the slapping apex beat were reflected in a characteristic pattern in the ballistocardiogram in the apical area. In the proto-systolic period there was an abnormally large downward deflection (PS), which was unrelated to atrial systole, since it was seen both in patients with sinus rhythm and atrial fibrillation. This was followed by a delayed large and steep upstroke (IC^1), coinciding with closure of the mitral valve, as indicated by the timing of the first heart sound in the simultaneous phonocardiogram (Fig. 9). The delay of the first heart sound, which is well known in mitral stenosis and usually measured in relation to the Q wave in the electrocardiogram, was immediately apparent in the ballistocardiogram in the abnormally wide and deep downward wave in the proto-systolic period, which measured 0·10 sec., as compared with 0·05 sec. in the normal subject. During ventricular proto-systole, the downward deflection PS indicated initial outward forces accompanying ventricular contraction. When left ventricular pressure finally

exceeded left atrial pressure, the mitral valve closed abruptly, giving rise to large inward forces, registered in the ballistocardiogram by the tall steep upstroke IC[1]. This sequence of forces was appreciated by the hand as a slapping beat.

The opening snap, as already described, coincided with the beginning of the downward deflection in the diastolic rapid inflow period. This downward deflection, often only clearly shown in records from the upper sternal area, was small and abnormally early. It was followed by an upward deflection, after which the tracing returned to the base-line. This sequence reflected early acceleration of ventricular filling, due to the high left atrial pressure, an acceleration that is then rapidly checked

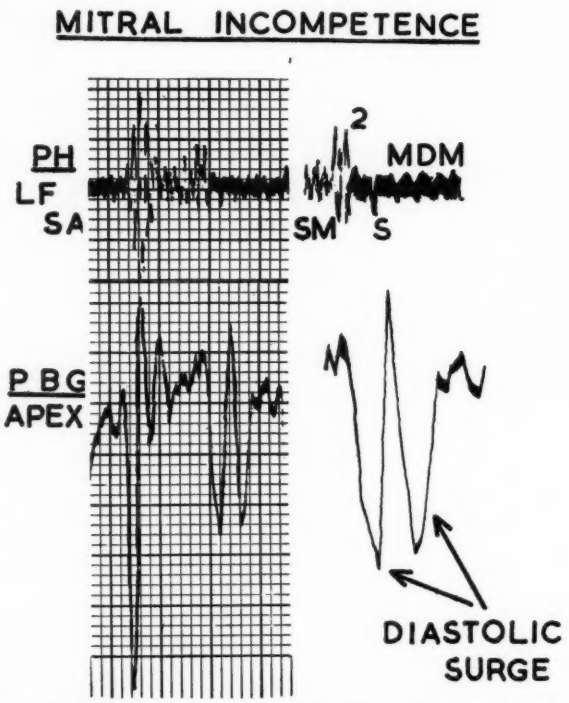

FIG. 10.—Dominant mitral incompetence of severe degree. Diastolic surge in rapid inflow period. SM = systolic murmur. S = snap. MDM = mid-diastolic murmur. At autopsy long diameter of mitral valve = 3 cm.; great left ventricular hypertrophy.

owing to the reduced maximum possible flow through the valve as a result of its stenosed orifice.

In severe *mitral incompetence* the salient feature of the ballistocardiogram was a very large bifid downward deflection in the diastolic rapid inflow period (Fig. 10). This was thought to result from large outward forces during the early diastolic surge of blood into the left ventricle, due to the high pressure in the left atrium at the end of systole. This diastolic surge was easily recognizable on palpation and was noted by Weitz (1917). It is the counterpart of the third heart sound in mitral incompetence, described by Brigden and Leatham (1953). The ballistocardiogram illustrated was of a patient with dominant mitral incompetence of severe degree, in whom the diagnosis was confirmed at autopsy.

In view of the striking difference in the ballistocardiogram in these examples of mitral stenosis

and incompetence, it is possible that the ballistocardiogram may provide an ancillary aid, helping to distinguish between dominant stenosis and incompetence.

In *tricuspid stenosis* the most marked features in the ballistocardiogram at the sternal area were the large deflections in atrial systole, coinciding with a palpable præcordial atrial beat, and the small amplitude of the deflection in the diastolic rapid inflow period (Fig. 11). In marked contrast to this were the large downward deflections in the rapid inflow period in *tricuspid incompetence* (Fig. 11).

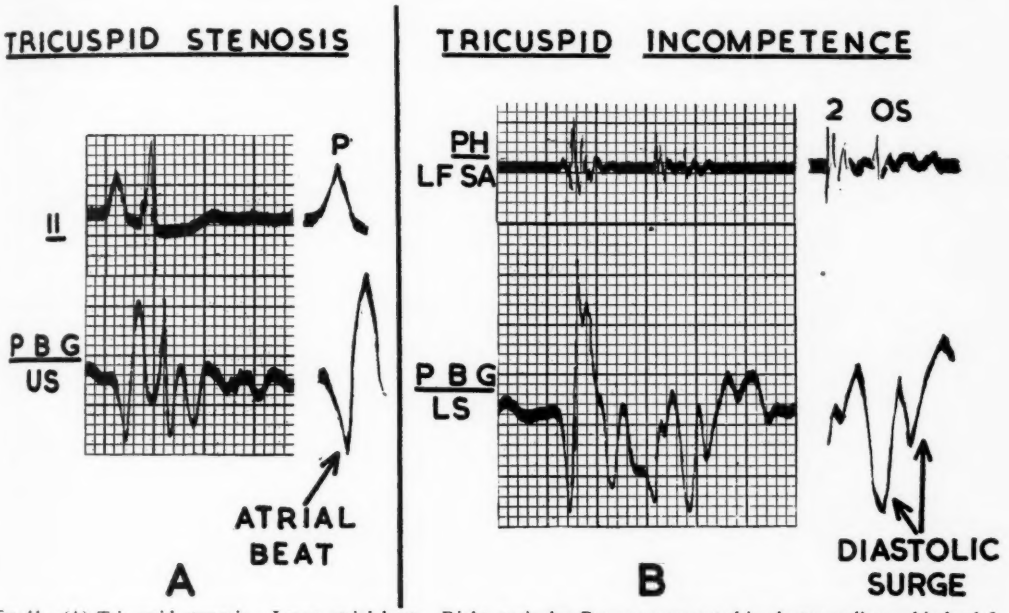

FIG. 11.—(A) Tricuspid stenosis. Large atrial beat. Right auricular P wave augmented in electrocardiographic lead 2. (B) Tricuspid incompetence, complicating mitral stenosis. Diastolic surge of tricuspid incompetence. OS = opening snap of mitral valve.

This difference between the ballistocardiogram of tricuspid stenosis and incompetence was thought to be due to the same factors operating in the right heart as operated in the left heart in mitral valve disease. As in mitral incompetence, the diastolic surge of tricuspid incompetence was readily palpable, being most marked in this condition at the left sternal edge, a physical sign noted by Volhard (1904). In contrast to mitral incompetence, on the other hand, in which the downward deflection in the diastolic rapid inflow period tended to decrease on inspiration, in tricuspid incompetence inspiration greatly increased the amplitude of this deflection.

SUMMARY AND CONCLUSIONS

Pulsation of the chest wall has been recorded by a new method using the accelerometer described by Elliott *et al.* (1954). By means of this instrument it has been possible to record acceleration ballistocardiograms at selected areas of the præcordium and to study their characteristics. Acceleration ballistocardiograms were studied in 20 healthy subjects. The direction of the main deflections was in general similar, whether the recording was made at the apical, upper sternal, or lower sternal areas, although the direction of certain deflections in late systole and early diastole was reversed at the upper sternal as opposed to the apical area.

The præcordial ballistocardiogram was found to give information about the sequence, direction and relative magnitude of the cardiovascular forces acting during the cardiac cycle and appeared to reflect to a large extent local forces in the heart superimposed upon the more general cardiovascular forces recorded in conventional ballistocardiography.

In order to assess the possible value of the ballistocardiogram as an ancillary diagnostic aid, a study was also made of this in examples of common diseases. In a patient with left heart failure due to hypertension, the heaving apex beat and quadruple rhythm were clearly seen in the ballistocardiographic pattern. The water-hammer apex beat of free aortic incompetence, the tapping beat and parasternal lift of atrial septal defect, and the slapping apex beat of mitral stenosis were also clearly reflected. The premature halting of diastolic rapid inflow of mitral stenosis contrasted with the diastolic surge of mitral incompetence, while similar information was obtained in disease of the tricuspid valve. In constrictive pericarditis halting of rapid ventricular filling was shown to become less abrupt after successful operation.

From this preliminary survey of examples of common diseases, the præcordial ballistocardiogram was seen to afford added information about the abnormal cardiovascular dynamics in each condition. In general it appeared to reflect the reaction of the heart to each disease rather than the disease itself. In addition, although not recording movement directly, it reflected the abnormal physical signs appreciated on inspection and palpation of the præcordium.

In conclusion præcordial ballistocardiography contributes to our knowledge of cardiovascular dynamics in health and disease, relates cardiovascular dynamic events to other phenomena, such as the heart sounds, depicts graphically information about the forces responsible for præcordial pulsation, and may prove of value, as an ancillary diagnostic aid, in helping to assess the relative degree of stenosis and incompetence in valvular disease of the heart.

I should like to express my sincere thanks to Dr. Robert V. Elliott, who generously presented the accelerometer with which this work was carried out, and also Dr. John R. Braunstein for his interest in this project and for introducing me to Dr. Elliott.

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LEGENDS

The illustrations have been retouched in places owing to the faintness of the more rapid deflections in the original Sanborn records.

General Key to Legends

PBG = præcordial ballistocardiogram.
LS and US=lower and upper sternal areas.
11 = electrocardiographic lead II.

PH = phonocardiogram.
LF and HF=low and high frequency.
MA, SA and PA=mitral, supramammary and pulmonary areas.
1, 2 and 3=first, second and third heart sounds.
A=atrial sound.

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INFLUENCE OF ACETYLCHOLINE ON THE PULMONARY ARTERIAL PRESSURE

BY

PETER HARRIS*

From the Cardiological Department, King's College Hospital

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It is still a matter for debate whether active variation in the calibre of the vessels of the pulmonary circulation can be caused by physiological or pharmacological stimuli. In most observations, the agents used to test the pulmonary circulation are known to have an effect also on the systemic circulation and often on the cardiac output. Under these circumstances the pulmonary arterial pressure is liable to be influenced by factors other than local alterations in the calibre of the vessels of the lesser circulation.

In an attempt to circumvent these difficulties, it was decided to study the effects of acetylcholine on the pressures in the pulmonary circulation in a group of patients. Ellis and Weiss (1932) demonstrated the destruction of acetylcholine in the blood stream in man by the lack of cumulative action during its prolonged intravenous infusion. They and also Carmichael and Fraser (1933) observed flushing of the head and upper part of the body when acetylcholine was injected in sufficient dosage into a vein, while intra-arterial injection caused a regional dilatation of arteries and arterioles but no general effects. Since acetylcholine is destroyed so rapidly in the blood stream, it might be possible to inject it into the pulmonary artery in such a dose that it was inactivated before reaching the systemic circulation (Tiffenau and Beauvallet, 1944). In this way it was hoped that any vasomotor effect of the drug would be confined to the pulmonary circulation.

In animals, the action of acetylcholine is most evident in the systemic circulation, where it causes widespread arterial vasodilatation irrespective of whether these vessels are supplied by the sympathetic or parasympathetic systems (Hunt and Taveau, 1906; Dale, 1914; Hunt, 1917*a* and 1917*b*). Reports of the activity of the drug in the pulmonary circulation, however, have been conflicting (Hunt, 1917*a*; Daly, 1932 and 1933; von Euler, 1932; Franklin, 1932; Gaddum and Holtz, 1933; Johnson *et al.*, 1937; Hamilton *et al.*, 1939; Petrovskaia, 1939; Foggie, 1940; Friedberg *et al.*, 1943; von Euler and Liljestrand, 1946; Dirken and Heemstra, 1948).

METHODS

Forty-seven patients were investigated. They had all been referred for diagnostic cardiac catheterization and had various disorders, which are given in Table I. Six of the children were anæsthetized with rectal pentothal: the remaining patients were conscious and received no premedication. All were in as near a basal state as possible. Three of the anæsthetized children had been given atropine.

A Cournand catheter was placed so that its tip lay in the main pulmonary artery. Between the hilt of the catheter and the head of the manometer was interposed a two-way tap with a short side-arm, through which a small volume of a solution of acetylcholine could be introduced into the lumen of the catheter. A recording of the pressure in the pulmonary artery was begun and, after an appropriate interval, the solution of acetylcholine was suddenly washed through the catheter into the pulmonary artery by means of a syringe filled with saline attached to the side-arm. With rapid manipulation of tap and syringe, the injection time was usually about two seconds. The recording of pressure was continued until the effects of the injection had disappeared or until it was apparent that there was no alteration in the pulmonary arterial pressure. In three cases the tip of the catheter lay in the right ventricle and then the right ventricular systolic pressure

* Work done during tenure of the Wiltshire Memorial Research Scholarship (1953–55) and submitted as part of a Ph.D. thesis at the University of London.

TABLE I

DETAILS OF EACH PATIENT AND THE EFFECTS OF ACETYLCHOLINE

Case No.	Sex and age (years)	Diagnosis	Before acetylcholine				Effects of acetylcholine				
			Pulmonary arterial pressure (mm. Hg)	PA mean pressure (mm. Hg)	Wedge pressure (mm. Hg)	Pulmonary "arteriolar" resistance (dynes. sec. cm.$^{-5}$)	Pulmonary arterial pressure	Wedge pressure	Systemic blood pressure	Cough	Heart rate
1	F 33	MS	57/28	44	30	180	0	+ 5	—	0	0
2	F 46	MS	115/50	77	41	820	−20/12·5	+2·5	—	0	0
3	F 43	PDA	140/10	59	5	270	−42·5/7·5	—	—	0	0
4	F 40	MS. MI	64/35	50	33	290	−12·5/10	+10	0	0	0
5	F 25	MS. AI	66/41	53	37	150	−12·5/7·5	—	—	0	0
6	F 33	MS	116/56	82	46	770	−20/10	—	0	0	0
7	F 8	Normal	34/18	24	13	—	0	—	—	0	0
8	M41	ASD	170/68	125	—	—	0	—	—	0	0
9	F 60	PI. Emphysema	68/25	44	—	—	−20/15	—	0	0	0
10	M 3	VSD†	85/52	70	14	—	−22·5/27·5	—	−10/10	0	0
11	M15	Normal	28/14	19	16	100	0	—	−20/10	+	+
12	M17	VSD	40/21	29	18	—	0	—	—	0	0
13	M25	MS	28/11	17	16	10	0	0	—	0	0
14	M39	MS	44/24	33	30	—	0	0	—	0	0
15	M56	MI. A fibr.	55/25	46	31	350	−12·5/0	—	—	0	0
16	F 38	MS	88/33	57	36	350	−15/10	—	0	+	+
17	M42	ASD	155/58	95	—	—	0	—	—	0	0
18	M39	Pulmo. Hypert.	105/47	67	—	—	−12·5/5	—	—	0	0
19†	F 45	MS. TI, A Fibr.	124/57	89	—	—	0	—	—	0	0
20	F 3	PDA. ASD	60/40	51	9	—	0	—	—	0	0
21	M 4	Cong. MS†	50/22	35	28	—	0	—	—	0	0
22	M50	Emphysema	39/22	30	13	330	0	0	0	0	0
23	F 40	Eisenmenger	140/55	93	4	—	0	—	—	+	+
24	F 30	MS	39/18	28	24	—	0	—	—	0	0
25	F 40	MS	100/73	84	32	480	−10/10	—	—	0	0
26	F 9	ASD	120/70	94	13	1550	0	—	—	0	0
27	F 11	ASD	29/17	22	12	130	0	—	—	0	0
28	F 16	MS	63/25	39	22	280	+5/10	—	—	+	+
29	F 29	MS	91/42	60	—	—	−25/5	—	—	+	+
30	M 8	Eisenmenger	93/58	74	7	—	+10/10	—	—	+	+
31	M29	Pulm. fibrosis	57/36	47	—	—	−12·5/5	—	−20/10	+	+
32	M11	Normal	35/19	26	13	150	0	—	—	0	0
33	F 30	MS	28/13	18	15	60	0	—	—	+	+
34	F 23	Pulm. hypert.	85/50	63	—	—	−20/15	—	—	0	0
35	M 7	VSD	26/13	20	13	—	0	—	—	+	+
36	F 48	MS	52/25	38	28	120	−20/10	—	0	0	0
37	F 24	MS	48/26	38	29	110	0	+10	—	0	0
38	F 40	MS	160/65	100	44	1210	0	0	—	0	0
39	F 40	MS. AI	38/20	27	20	80	0	0	—	0	0
40	F 30	MS	108/39	77	—	—	−50/*	—	—	0	0
41	F 21	MS	38/20	29	20	140	0	—	—	+	+
42	M39	Atrial fibr.	32/21	27	—	—	0	—	—	0	0
43	F 40	MS. AF	51/42	47	33	290	0	—	—	0	0
44	F 53	ASD	56/21	44	14	160	0	—	—	0	0
45	M30	Pulm. hypert.	113/57	80	11	1780	0	—	—	0	0
46	F 34	MS	83/31	50	28	260	−12·5/*	—	—	0	0
47	M49	MS	73/38	50	34	280	−15/*	—	—	0	0

* Right ventricular pressure.
† Patient given atropine

was taken as indicating the pulmonary arterial systolic pressure. In some patients a double-lumen catheter was used. Acetylcholine was then injected through the side-opening of the catheter and thus arrived in the right ventricle while the pressure in the main pulmonary artery was recorded from the terminal opening.

In nine patients the pulmonary artery wedge pressure was measured via the terminal opening of a double-lumen catheter while acetylcholine was injected into the pulmonary artery via the side opening. In each of these cases, the recording of a true wedge pressure was verified by the shape of the tracing and by the withdrawal of highly oxygenated blood. In nine patients a recording of pressure in a systemic artery was made during the injection of acetylcholine into the right ventricle or pulmonary artery.

The dose of acetylcholine varied from 0·25 to 8·0 mg. In those patients in whom an effect was observed, the average effective dose given was 2·3 mg. When the effect on the systemic arterial pressure was being observed, the dose of acetylcholine was the maximum that had been used in studying the pressures in the pulmonary circulation in the same patient. There were no recordings of pressure simultaneously in the pulmonary artery or pulmonary wedge position and systemic artery.

Pressures were measured by means of a capacitance manometer, using a direct writing recording apparatus (Bareham). Zero was taken at the level of the table on which the patient lay. In the control observations taken before injection of the drug, the average levels of systolic and diastolic pressures in the pulmonary artery were read during two or more respiratory cycles and the mean pressure was measured by means of planimetry over a similar period of time. The rapid alterations in pressure following the injection of acetylcholine did not allow of so accurate a measurement. In most instances, also, reduced paper speed at this time did not permit measurement of mean pressures. Observations of pressures following the injection of the drug are therefore limited to systolic and diastolic levels and these are given to the nearest 2·5 mm. Hg. Variations in pressure were ignored if they could not be repeated, using the same dose of acetylcholine, after an interval of five minutes.

The evanescent effect of the drug on the pulmonary arterial pressure would have made any simultaneous measurement of pulmonary blood flow impracticable. By using continuous infusions of acetylcholine, it might have been possible to have reached a steady state during which estimations of pulmonary blood flow would have been most valuable. However, the apparatus for carrying this out with sufficient accuracy was not available. In the assessment of resting pulmonary arteriolar resistance made before the injection of acetylcholine, the oxygen uptake was measured from the slope of a spirometric tracing.

Results

A brief reference to these results has been made previously (Harris, 1955*a*). Details of each patient are given in Table I.

Pulmonary Arterial Pressures. In twenty-seven patients there was no alteration in the pressure in the pulmonary artery after the injection of acetylcholine. In two there was a slight rise in pressure, but in both this was accompanied by coughing and tachycardia. In eighteen patients, acetylcholine caused a transient fall of varying degree. Fig. 1 shows recordings from a patient in whom the fall was particularly apparent and gives an indication of the reproducibility of the effect. Only in Case 36 was the pressure in the pulmonary artery reduced to within the normal range. The fall in pressure would usually start three or four seconds after the injection and reach its greatest

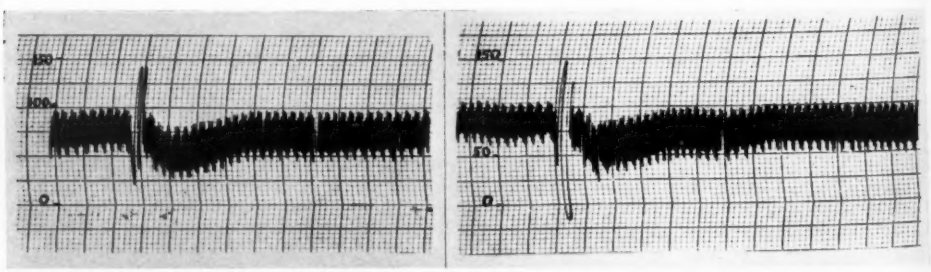

Fig. 1.—Recordings of pulmonary arterial pressure in Case 10. The time of injection of acetylcholine coincides with the sudden wide movements of the recording pen just prior to the fall in pressure. On each occasion, the dose of acetylcholine was 0·25 mg. injected into the pulmonary artery. One major horizontal division represents approximately 7 sec. The scale of pressures is in mm. Hg.

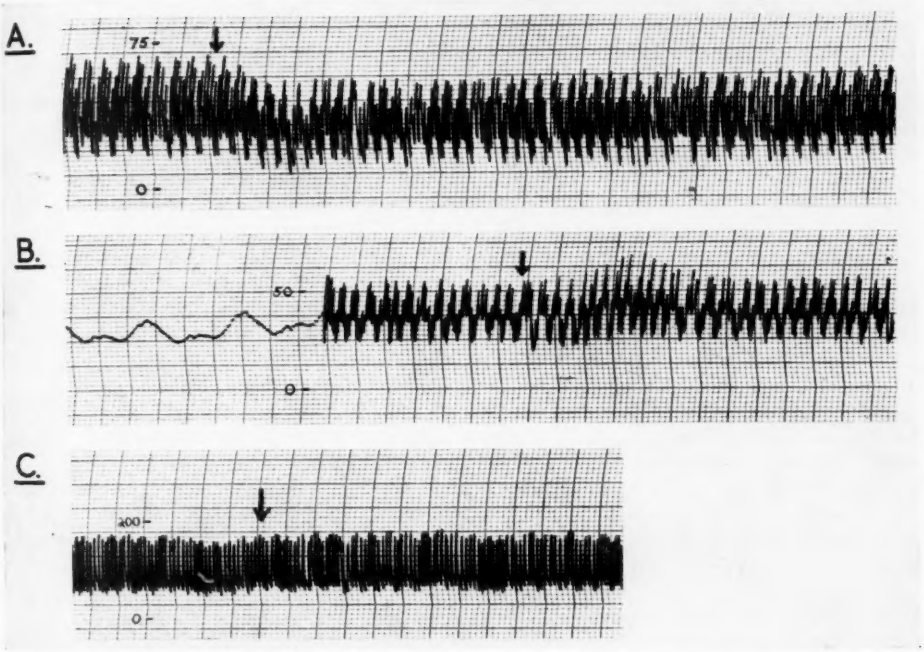

FIG. 2.—The effects of injection of 2 mg. acetylcholine in Case 4. (A) Pulmonary arterial pressure. (B) Wedge pressure. (C) Brachial arterial pressure. The arrows indicate the start of the injection. One major horizontal division represents approximately 7 sec. The start of tracing (B) is at a fast rate to show the wedge curve; at this point, each major horizontal division represents 0·2 sec. The scale of pressure is in mm. Hg.

degree after ten to twenty seconds. The subsequent rise was not so abrupt and might even be prolonged for several minutes (Fig. 2).

Pulmonary Artery Wedge Pressure. In five patients there was no change in the wedge pressure after injection of acetylcholine into the pulmonary artery: in four there was a slight but distinct transient rise (Fig. 2). In the five cases where the wedge pressure was unchanged, the pulmonary arterial pressure was also unaffected by acetylcholine. Of the four cases where the wedge pressure was found to rise, two showed a fall and two showed no change in pulmonary arterial pressure when acetylcholine was injected into the right ventricle. All except one of these nine had mitral stenosis.

Systemic Arterial Pressure. There was no change in the systemic arterial pressure in six, and a transient fall in three patients following the injection of acetylcholine into the right ventricle or pulmonary artery. These nine patients tended to be taken more frequently from those in whom acetylcholine had caused a fall in pressure in the pulmonary artery, since information was being especially sought on how much the fall in pulmonary arterial pressure could be caused by vasodilatation in the systemic circulation. Thus, in seven of them there had been a fall in pulmonary arterial pressure following injection of the drug. Of these seven, only two showed a fall in systemic arterial pressure due to acetylcholine. Of the remaining two in whom the pulmonary arterial pressure had not responded to acetylcholine, the systemic arterial pressure fell in one and was unchanged in the other.

Other Effects. Coughing and tachycardia occurred in many patients when higher doses of acetylcholine were given. These two symptoms occurred together. Often associated with the

desire to cough was an irritating or burning feeling in the throat or deep inside the chest. On two occasions, the respiratory variation in intravascular pressure in the chest was found to increase following the injection of acetylcholine and this was thought to indicate constriction of the bronchioles. Transient bradycardia such as was described by Carmichael and Fraser (1933) was observed only once. Tachycardia following acetylcholine was, however, common and might persist for several minutes. Abnormality of the electrocardiogram was observed only once when two ventricular premature beats followed the injection, which had been made into the right ventricle. No patient complained of flushing or burning of the skin and, since the investigation was carried out in a red light, it was not possible to observe any reddening of the skin. In no patient did the injection of acetylcholine give any cause for alarm.

In three patients in whom a fall in pulmonary arterial pressure had been caused by the injection of acetylcholine, a similar injection of saline carried out with the same ritual caused no alteration in pressure in the pulmonary artery. The effects of coughing, by itself, on the pulmonary arterial pressure were not comparable with those due to acetylcholine.

Discussion

From the results quoted above, the pressures in the pulmonary circulation in the majority of cases did not respond to acetylcholine. About one in every three patients, however, showed a transient fall in pulmonary arterial pressure following the injection of the drug, an effect that does not seem to be related to the fall in pressure sometimes found in the systemic arteries. When the wedge pressure has been affected, it has risen. Probably, in these cases, the brief rise in wedge pressure has been made more apparent by the presence of mitral stenosis which was present in all and would delay the speed with which the left ventricle could restore the left atrial pressure.

A fall in pulmonary arterial pressure accompanied by a rise in wedge pressure cannot be accounted for by a reduction in pulmonary blood volume due to systemic vasodilatation. Neither would bronchoconstriction be expected to have this effect on the pressures in the pulmonary circulation. A reduction in cardiac output is unlikely to have given rise to so immediate a fall in pulmonary arterial pressure, but in the absence of measurement this must be accepted as possible. The fall in pulmonary arterial pressure has not been due to a bradycardia such as was observed in dogs by Johnson *et al.* (1937).

There would seem, therefore, to be strong indications that acetylcholine has caused a vasodilatation in the branches of the pulmonary artery. Why, however, should such vasodilatation occur in some patients and not in others? A clue to the answer may be given by the histogram in Fig. 3 where the patients are arranged according to the mean pulmonary arterial pressure that had been measured before giving the drug. When the pressure in the pulmonary artery was normal, a fall in pressure following the injection was never found. As the mean pressure in the pulmonary artery rose, there was a gradual increase in the proportion of patients showing a fall in pressure until, between mean pressures of 50–70 mm. Hg, almost every case showed a response. Thereafter, the proportion of patients showing a response fell off and all the patients within the higher ranges of pulmonary arterial pressure were once more unresponsive.

This peculiar distribution of the responsive group within the total series of patients has been tested by means of the χ^2 test, and would arise by chance less often than once in a hundred times. Further analyses, the details of which are given elsewhere (Harris, 1955*b*), showed that the type of disease or the age or sex of the patient had no specific influence on the action of acetylcholine. It seems, therefore, that the responsiveness of the pulmonary circulation to the action of acetylcholine is related in a distinctive way to the initial level of pressure in the pulmonary artery.

The wide differences in pulmonary arterial pressure that occur between the various patients are mainly due to differences in the resistance of flow offered by the smaller branches of the pulmonary artery, so that the effects of acetylcholine are most probably related primarily to the nature of the resistance occurring at this level. The development of pulmonary arterial hypertension is accompanied by distinctive changes in the structure of the small pulmonary arteries. Thus, the

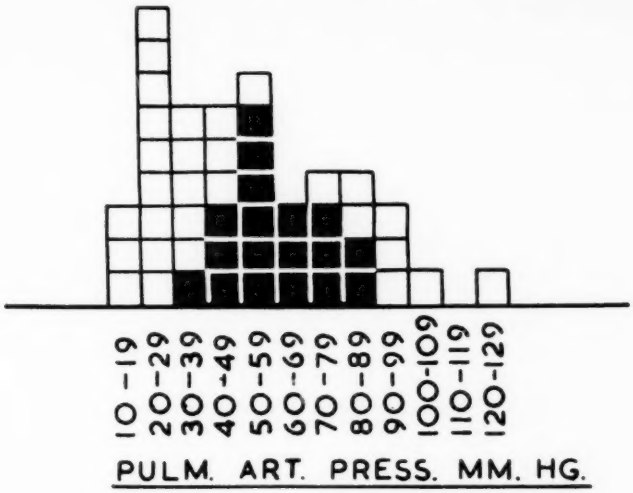

FIG. 3.—Histogram, showing the patients arranged according to the level of the initial mean pressure in the pulmonary artery. Each black square indicates a patient in whom the pressure in the pulmonary artery fell after acetylcholine had been given. Each white square represents a patient in whom it did not show such a fall.

responsiveness or unresponsiveness of these vessels and the degree of resistance that they offer to flow may well both be linked to the anatomical differences to be found in their walls.

Unfortunately, no such direct comparison between function and structure can be made in these patients, since the microscopical structure of the small pulmonary arteries is known in only three of them. On the other hand, the special relationship of the response to acetylcholine to the level of pulmonary arterial pressure seems not to be a matter of chance, and it may therefore be allowable to compare this functional relationship with the variations in structure that are known to occur in the small pulmonary arteries during disease.

In this comparison, the alterations in structure of the media of the small pulmonary arteries would be expected to be of prime importance, since any sudden variations in the calibre of these vessels are most likely to be due to a change in the tone of the muscle contained in their walls. Normally, the small pulmonary arteries are only meagerly provided with muscle (Brenner, 1935), but, in those diseases where pulmonary hypertension occurs, a thickening of the medial muscle of these vessels has been frequently observed (Parker and Weiss, 1936; Civin and Edwards, 1950; Selzer and Laqueur, 1951; Henry, 1952; Brown *et al.*, 1955). It is likely that such hypertrophy is in itself evidence of an active vasoconstriction occurring intermittently or continuously for a prolonged time (Harris, 1955*a*). Eventually, however, fibrosis develops in the walls of the small pulmonary arteries, tending to replace the muscular tissue (Kaump and Dry, 1938; Larrabee *et al.*, 1949).

It may be possible, therefore, to explain the relationship of the effects of acetylcholine on the pulmonary circulation to the level of the pulmonary arterial pressure in terms of these two overlapping processes of muscular hypertrophy and fibrosis which take place in the walls of the small pulmonary arteries. When the pulmonary arterial pressure is normal, the muscle of the media of these vessels is thin and its tone slight, so that the response to acetylcholine is too feeble to have any substantial effect on the pressure in the pulmonary artery. When the pulmonary arterial pressure becomes raised, the medial muscle becomes hypertrophied and its tone is probably increased: the activity of acetylcholine will then become increasingly apparent since the muscular coat is capable of more effective contraction and relaxation. Finally, with predominant fibrosis the small pulmonary arteries gradually become rigid tubes, once more unable to respond to the drug.

Other factors might influence these effects of acetylcholine at different levels of pressure. It is likely, for instance, that in normal people the effects of vaso-active drugs on the pressure in the pulmonary artery

are reduced by the opening or closing of alternative channels for the passage of blood through the lungs. This cushioning effect may gradually be lost in the presence of an increasing pulmonary hypertension since it is possible that the level of pressure in the pulmonary artery then comes to exceed by an increasing amount the critical opening and closing pressures of the small arterial branches. Further, although the same fractional change in resistance should produce an equal fractional change in pulmonary arterial pressure, yet the absolute change in pulmonary arterial pressure will naturally increase as the initial level of pressure becomes higher. Further, it might be argued that subintimal thickening, by encroaching upon the size of the lumen of a small pulmonary artery, would actually magnify any fractional alterations in the size of the lumen following activity of the media. All of these factors could play a part in increasing the effects of acetylcholine in pulmonary hypertension, though none can explain the final diminution of the effect of acetylcholine when the pulmonary arterial pressure becomes extremely high.

The exact way in which acetylcholine might cause pulmonary vasodilatation is not revealed by these observations. Its rapid action on the pulmonary arterial pressure suggests that vasodilatation in the pulmonary circuit is most probably due to a direct influence of the drug on the muscle fibres in the walls of the vessels. One of the three patients who had been given atropine had a substantial fall in pulmonary arterial pressure after acetylcholine, and it seems likely, therefore, that the doses of acetylcholine used were but little inhibited by a therapeutic concentration of atropine in the tissues.

Summary

The rapid injection of acetylcholine into the pulmonary artery or right ventricle has caused a transient fall of the pulmonary arterial pressure in 18 of 47 patients with various abnormalities. There is strong evidence that this fall was due to vasodilatation in the periphery of the pulmonary arterial tree. The response to acetylcholine was related to the initial level of pulmonary arterial pressure in a distinctive manner. It was found most frequently in patients with a moderate rise of pulmonary arterial pressure and did not occur when this was normal or when it was greatly raised. These results may be related to the structural alterations that occur in the small pulmonary arteries in association with pulmonary hypertension.

I am most grateful to Dr. Terence East for advice and encouragement.

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THE EFFECT OF ACETYLCHOLINE ON PULMONARY VASCULAR RESISTANCE AND LEFT ATRIAL PRESSURE IN MITRAL STENOSIS

BY

PAUL WOOD, E. M. BESTERMAN, M. K. TOWERS, AND M. B. McILROY

From the National Heart Hospital and the Institute of Cardiology, London

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In mitral stenosis the obstruction to the circulation leads to a build-up of pressure in the left atrium which averages about 25 mm. Hg in uncomplicated cases with critical stenosis requiring valvotomy (orifice 10×5 mm. or less). On effort the cardiac output increases and the left atrial pressure rises well above the osmotic pressure of the plasma, even up to 50 or 60 mm. Familiar consequences of this situation include hæmoptysis, frank pulmonary œdema, and chronic interstitial œdema of the lungs.

As a rule, the pulmonary artery pressure rises passively and maintains a more or less normal pulmonary arterio-venous pressure gradient of about 10 mm. (Fig. 1). The pulmonary vascular

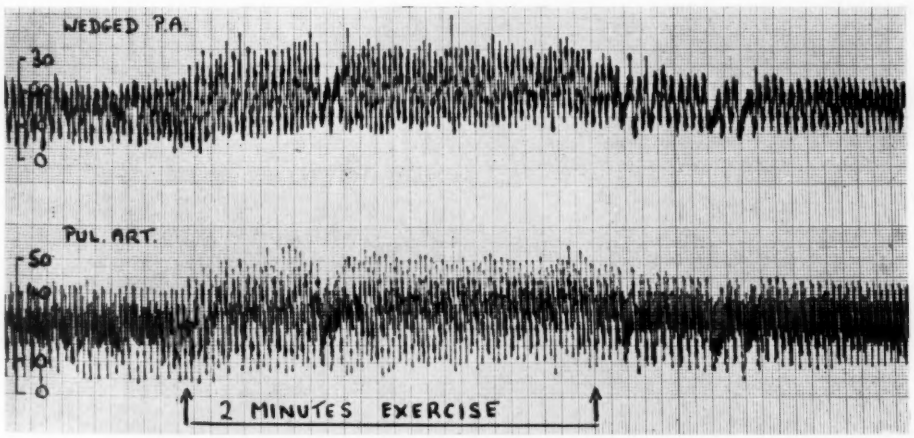

FIG. 1.—Passive pulmonary hypertension occurring on exercise in a case of mitral stenosis.

resistance in these simple cases of passive pulmonary hypertension is 0·5 to 5 units (40–400 dynes sec./cm.$^{-5}$). In a relatively small but important group of cases, however, pulmonary hypertension is of a different order and bears little relationship to the left atrial pressure, being due to intense pulmonary vasoconstriction (active pulmonary hypertension) or to widespread obstructive or obliterative changes in the small pulmonary arteries and arterioles (obstructive or obliterative pulmonary hypertension). Thus, in our own series of 350 cases of mitral stenosis subjected to valvotomy, the pulmonary vascular resistance was high (6–10 units) in 15 per cent and extreme (10–30 units) in 14 per cent. The cases with an extreme resistance behaved differently from

uncomplicated cases of mitral stenosis, and suggested that a sufficiently high resistance protected the pulmonary capillaries and venous radicles from developing dangerously high pressures, even in the presence of an orifice as small as 5×3 mm. Hg (Lewis *et al.*, 1952; Wood, 1954). The chief evidence on which this conclusion was based may be recapitulated as follows.

(1) A history of pulmonary apoplexy was obtained in 25 per cent of uncomplicated cases of mitral stenosis, but in only 12 per cent of those with a high resistance; recent congestive hæmoptysis occurred in 16 per cent of uncomplicated cases, but in only 4 per cent of those with a high resistance.

(2) Pulmonary œdema occurred in 10 per cent of the series. The pulmonary vascular resistance averaged 2·9 in these cases and never exceeded 5·2 units; in cases of equal or greater severity with no history of pulmonary œdema or paroxysmal cardiac dyspnœa or orthopnœa, the resistance averaged 9·2 units.

(3) Radiological evidence of chronic interstitial œdema of the lungs bore an inverse relationship to the pulmonary vascular resistance (Fig. 2). Typical skiagrams, one from a relatively low and the other from a high resistance case, are illustrated in Fig. 3 and 4.

(4) In cases of more or less equal severity in respect of the degree of stenosis, the left atrial pressure itself was also inversely related to the pulmonary vascular resistance (Fig. 5). The mechanism was attributed to the damping effect of a high resistance on the cardiac output (Fig. 6).

That functional pulmonary vasoconstriction plays an important part in initiating and maintaining the high resistance was suggested by the absence of a previous history of pulmonary

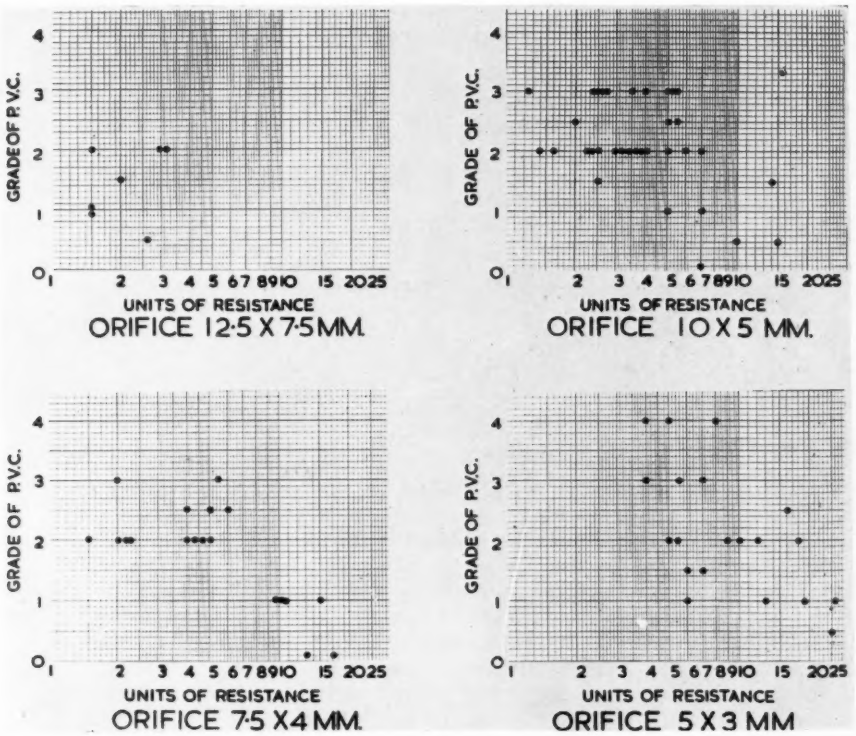

FIG. 2.—Chart, showing an inverse relationship between pulmonary venous congestion and the pulmonary vascular resistance in cases of mitral stenosis.

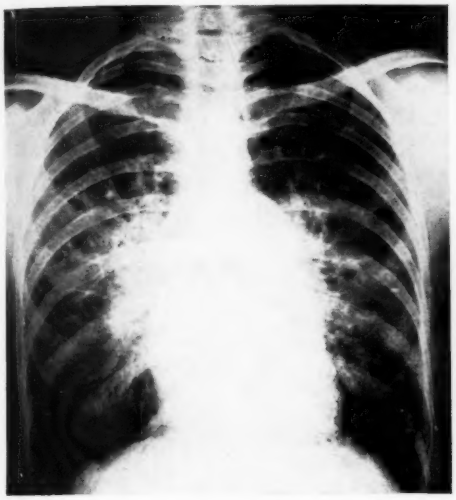

FIG. 3.—Skiagram, showing chronic interstitial œdema of the lung (pulmonary venous congestion) in a case of mitral stenosis.

FIG. 4.—Skiagram of a case of mitral stenosis with an extreme pulmonary vascular resistance, showing minimal pulmonary venous congestion.

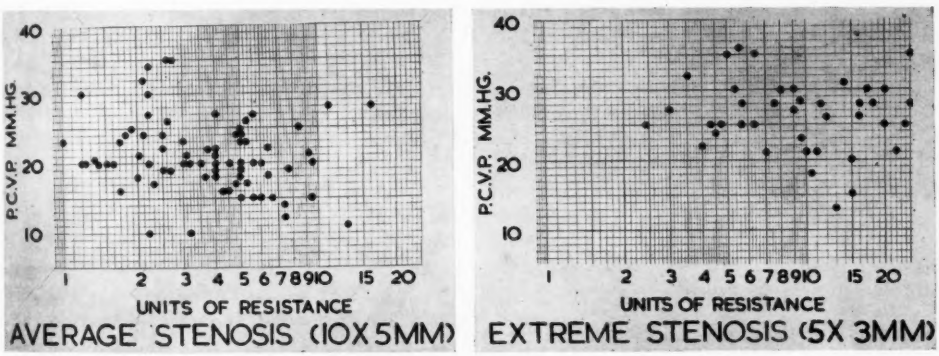

FIG. 5.—Chart, showing an inverse relationship between the mean left atrial pressure and the pulmonary vascular resistance in cases of mitral stenosis.

congestive symptoms in 80 per cent of the cases, by the fact that the average age of high resistance cases (39 years) was no higher than that of relatively low resistance cases with an equivalent degree of stenosis (39 years), and by extensive clinical and physiological evidence that the resistance commonly fell greatly after technically successful valvotomy.

The present paper deals with an attempt to test both parts of the thesis experimentally. If the concept that a high pulmonary vascular resistance is protective in the sense previously defined is correct, then lowering the resistance should result in raising the left atrial pressure and the cardiac output; secondly, if active pulmonary vasoconstriction is playing the part assigned to it, then the administration of a suitable pulmonary vasodilator should result in an appreciable fall in resistance. Ideally, the pulmonary vasodilator should be as selective as possible, so that it does not alter pulmonary or systemic venous tone or the systemic peripheral resistance. It was believed that

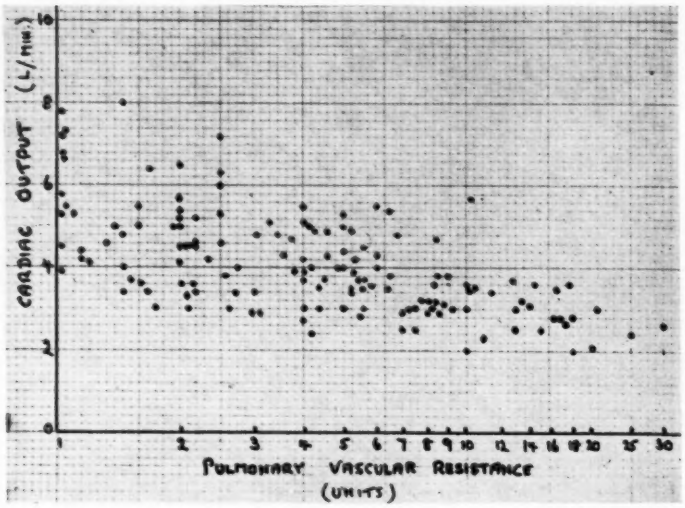

FIG. 6.—Chart, showing the braking effect of a high pulmonary vascular resistance on the cardiac output in cases of mitral stenosis.

acetylcholine might fulfil these criteria if injected directly into the pulmonary artery in a dose large enough to dilate the small pulmonary arteries and arterioles, yet small enough to be inactivated by the time it reached the systemic circulation. In fact this selective effect was usually achieved with a dose of 1 to 1·5 mg.

Method. A double lumen catheter was passed into the pulmonary artery so that the opening of the proximal barrel lay just distal to the pulmonary valve. Acetylcholine injected through this proximal barrel was expected to pass into both left and right pulmonary arteries. The proximal barrel was also used to obtain samples of mixed venous blood from the pulmonary trunk. The opening of the distal barrel lay well out in one or other pulmonary artery, but never far enough to wedge, so that the pulmonary artery pressure could be measured through this barrel. A second single lumen catheter was used to obtain the wedge pressure (Fig. 7). Two Riley needles were inserted into suitable arteries, one to record the systemic blood pressure, the other to obtain arterial samples. Oxygen consumption was measured by collecting 3 or 5 minute samples of expired air in a Douglas bag 5 minutes before, immediately after, and 5 minutes after the injection, two sets of simultaneous arterial and pulmonary artery samples being obtained during each period. In view of its instability acetylcholine was freshly prepared immediately before it was required. The initial dose was usually 1 mg. and was injected abruptly. If this proved insufficient to lower the pulmonary artery pressure appreciably, the procedure was repeated using 1·5 mg., and if there was still no effect 2 mg. was given. The usual critical dose was 1·5 mg. In view of the rapid inactivation of acetylcholine tests could be repeated, if necessary, within a few minutes.

RESULTS

Three cases of primary pulmonary hypertension served to demonstrate the selective action of acetylcholine so administered. Its effect in these three cases was similar (Fig. 8 and 9). The pulmonary artery pressure fell by an average of 37/20 mm. Hg, to a little over half the original pressure; the cardiac output rose by 0·5 to 1·0 litre per minute (15–20%); the pulmonary vascular resistance fell from an average of 12·3 units to an average of 6·6 units. In two of the cases the systemic blood pressure rose 15/5 mm., and the heart rate slowed 10 to 15 beats per minute; in the third case the blood pressure fell 3/5 mm. Hg indicating a slight systemic effect.

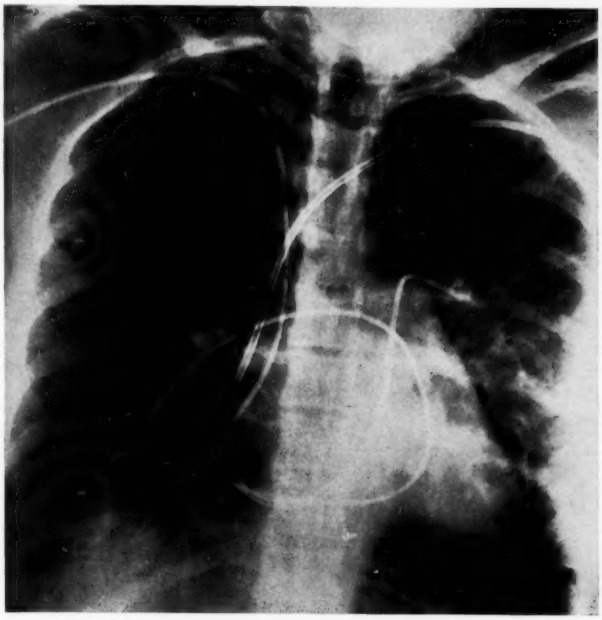

FIG. 7.—Skiagram, showing a double lumen catheter with its tip in the left pulmonary artery and the end of the proximal barrel just beyond the pulmonary valve; a single lumen catheter is wedged in a peripheral branch of the right pulmonary artery.

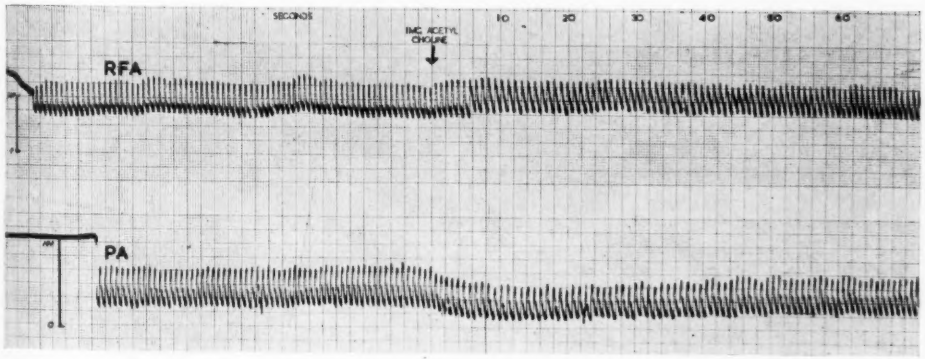

FIG. 8.—Pressure pulses from the pulmonary artery and femoral artery in a case of primary pulmonary hypertension, illustrating the typical response to acetylcholine.

Nine cases of mitral stenosis were studied (see table). In two there was no effect. The pulmonary artery pressure fell in each of the other seven, the drop averaging 15/8 mm. Hg; simultaneously the wedge pressure rose 3 to 5 mm. in the five cases in which it was recorded: the catheter could not be wedged in the other two, owing to lack of sufficient tapering—a common difficulty in cases with a high pulmonary vascular resistance. Two typical graphs are illustrated (Fig. 10 and 11). The pulmonary vascular resistance fell from an average of 9·4 units to an average of 5·4 units.

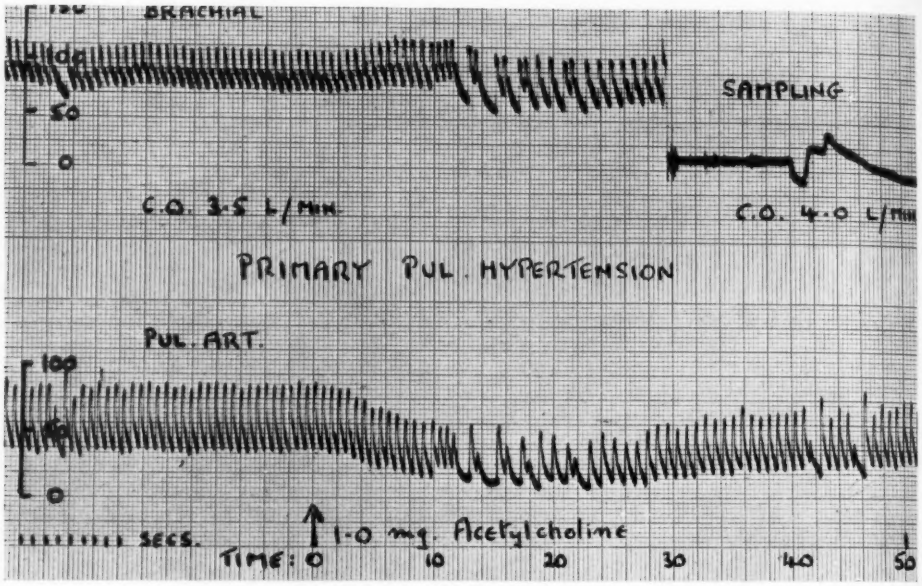

FIG. 9.—Pressure pulses from the pulmonary and brachial arteries in a case of primary pulmonary hypertension, showing a large fall in pulmonary vascular resistance following the injection of acetylcholine; the secondary fall in brachial artery pressure is due to a slight systemic effect of acetylcholine which in this case has not been totally inactivated during its passage through the lungs. Time in seconds.

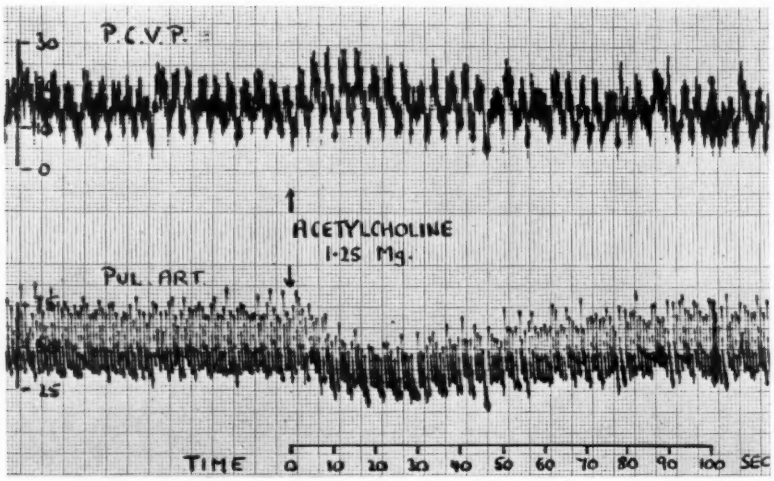

FIG. 10.—Simultaneous pulmonary artery and indirect left atrial pressure tracings from a case of mitral stenosis, showing a rise in left atrial pressure as the pulmonary vascular resistance falls.

The systemic blood pressure rose 5–10 mm. in three cases, and fell by a similar amount in two, presumably as a result of insufficient inactivation of acetylcholine. It did not change in the two in which the pulmonary artery pressure did not fall, and it was not recorded in the other two.

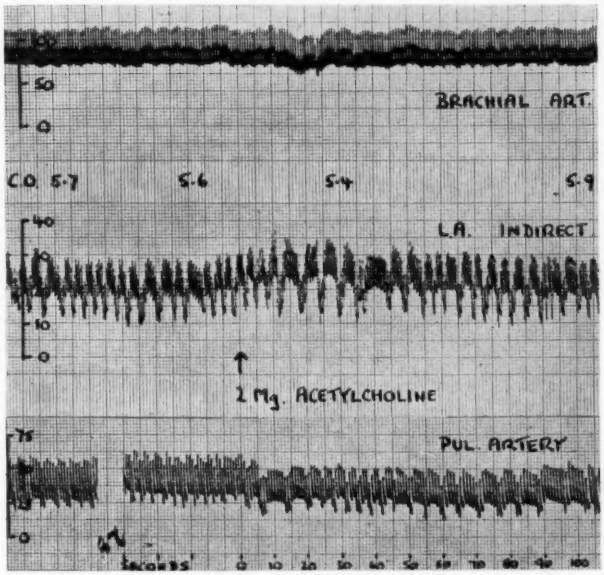

FIG. 11.—A second example, showing the effect of acetylcholine on pulmonary artery and left atrial pressure pulses in a case of mitral stenosis.

No convincing change in cardiac output was demonstrated, but it is difficult to measure small transient changes in output by means of the Fick principle. When the systemic blood pressure rises after acetylcholine, however, a rise of output may be assumed; and when there is no change of heart rate a rise in left atrial pressure must be followed by a rise of output. In fact, the heart rate did not alter except in one case in which it fell from 84 to 72 beats a minute.

TABLE I

EFFECT OF ACETYLCHOLINE ON NINE CASES OF MITRAL STENOSIS

Case	Dose (mg.)	Pul. vasc. resistance (units)		Pulmonary arterial pressure (mm. Hg)		Indirect (wedge) left atrial pressure (mm. Hg)		Cardiac output (l/min.)		Systemic blood pressure (mm. Hg)		Heart rate per. minute	
		before	after	before	after	before	after	before	after	before	after	before	after
1	1·0	4·8	2·0	55/25	40/17	17	—	3·7	—	180/100	—	108	104
2	1·0	4·5	4·5	50/30	50/30	14	14	6·0	6·0	100/60	100/60	69	72
3	1·5	17·0	17·0	120/60	120/60	—	—	—	—	130/70	130/70	48	48
4	2·0	9·0	5·5	45/25	40/20	13	16	2·2	—	120/60	—	72	72
5	2·0	2·5	1·3	60/32	50/27	22	28	5·6	5·9	115/75	100/60	72	72
6	1·5	5·0	3·7	80/45	65/38	21	25	6·3	—	120/70	125/75	66	66
7	1·0	16·0	12·0	133/50	113/38	27	30	3·1	3·0	160/105	170/110	96	96
8	1·25	12·0	9·0	87/37	75/30	20	—	3·0	—	120/60	112/60	84	72
9	1·25	14·0	4·0	75/38	50/25	20	24	2·6	2·4	120/65	125/70	78	78

SUMMARY AND CONCLUSIONS

We have recapitulated the reasons for believing that a high pulmonary vascular resistance in cases of mitral stenosis is initially functional and protects the pulmonary venous system from developing dangerously high pressures.

A method was devised for testing the thesis experimentally. Acetylcholine in doses of 1 to 1·5 mg. proved to be a powerful selective pulmonary vasodilator when injected directly into the pulmonary artery, and was virtually inactivated by the time it reached the systemic circulation.

Release of pulmonary vasoconstrictor tone halved the pulmonary vascular resistance in three cases of primary pulmonary hypertension; simultaneously the cardiac output and blood pressure rose.

In mitral stenosis a similar large fall in pulmonary vascular resistance was usually observed, and simultaneously the left atrial pressure rose. There was little change in cardiac output, blood pressure, and pulse rate.

It is concluded that in mitral stenosis the high pulmonary vascular resistance is at least partly functional, and is protective in the sense defined. Whether the reaction is purposeful or accidental is irrelevant to the thesis.

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CASE REPORTS

BALL-VALVE MITRAL OBSTRUCTION BY A SARCOMA OF A PULMONARY VEIN

BY

A. R. R. CUMMING AND A. J. SHILLITOE

From the Kingston General Hospital, Hull

Primary tumours of major blood vessels are rare. Giaccai (1949), in his review of reported cases found 9 benign tumours, one of which was an enchondroma of a superficial vein of the forearm, and 17 malignant tumours, four of which were sarcomata of the pulmonary artery, and one (Ausbüttel, 1939) from the right pulmonary vein. This latter had the structure of a pleomorphic-celled sarcoma, proliferated as far as the left atrium, and gave rise to an implantation metastasis on the anterior mitral leaf. Ravid and Sachs (1943), reported a primary myxosarcoma of the left auricle and pulmonary vein associated with multiple tumours of various types elsewhere in the body. We report here a tumour of the right superior pulmonary vein which grew into the left atrium and occluded the mitral opening.

Case Report

W. H., a 47-year-old farmer, was quite fit until October, 1954, when he had a febrile respiratory illness with hæmoptysis. There were no physical signs in the chest or signs of recent thrombophlebitis. X-rays showed a small hazy shadow in the right mid-zone. He recovered and returned to work but was readmitted with hæmoptysis the following month. The shadow was now resolving and physical and cardiographic examinations were negative. Subsequently he felt well apart from an ache in the right side of the chest.

Four months after his first illness he was readmitted to hospital with persistent hæmoptysis and extreme dyspnœa accompanying attacks of coughing. He was cyanosed and the physical and radiological signs were those of pulmonary œdema. His pulse was very rapid and small and he showed intermittent auricular fibrillation. The first sound at the mitral area had a slapping quality. He died within a few hours.

Necropsy Findings. There was some congestion of the bronchi and lower part of the trachea and both lungs were congested and œdematous. About 500 ml. of faintly brownish fluid were present in the left pleural cavity. The right pleural cavity was almost obliterated by old adhesions but nevertheless contained some excess fluid. The liver showed a slight nutmeg pattern. The spleen was a little enlarged. The major arteries had only a few small flecks of atheroma. All other organs except the heart were normal.

Heart. The left atrium was found to be filled by a tumour measuring 5·0 cm. in maximal diameter (Fig. 1). It had a slightly roughened surface and bulged into the mitral orifice. The pericardium, myocardium, endocardium, and valves were normal. Further dissection showed that the tumour arose from a small pedicle in the right superior pulmonary vein between 2 and 3 cm. away from the vein's junction with the left atrium. It almost occluded the lumen of the vein and in many places was adherent to the intima. This adherence was only slight and separation could easily be effected by gentle stripping except at two sites, one at the veno-atrial junction, and the other shortly after its origin, where the attachment was firm. In parts the tumour was fairly soft, but most of it was hard and could not be cut with a knife.

Microscopically it was found that the pedicle was composed of collagen, a few elastic fibres, and material that was metachromatic with toluidine blue and removable by hyaluronidase. Adjacent to its pedicle the growth consisted of well formed non-malignant osseous tissue but this rapidly gave place to an osteogenic sarcoma which constituted its remainder (Fig. 2). At the veno-atrial junction there was invasion of the intima of the vein and atrium but this did not penetrate beyond the elastic lamina. At the other site of firm attachment the growth penetrated through the vein wall and spread to a slight extent in the surrounding

lung tissue. A blood vessel supplying the tumour opened at the base of the pedicle and can be seen in Fig. 3. Elsewhere the blood supply seemed to be derived from vessels opening directly on the surface.

At the point of origin of the pedicle the pulmonary vein received a tributary which was not normal: this tributary was excessively convoluted and had marked fibroelastic thickening of its intima. Other blood vessels in the lungs seemed satisfactory except for a few on the right side which showed evidence of thrombosis and recanalization. Both lungs were congested.

FIG. 1.—Interior of heart, showing polyp obstructing mitral orifice.

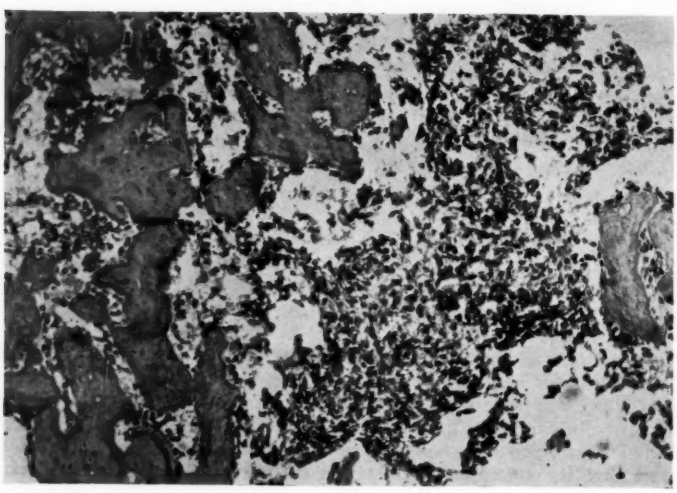

FIG. 2.—Osteosarcomatous tissue. Hæmatoxylin and eosin: ×85.

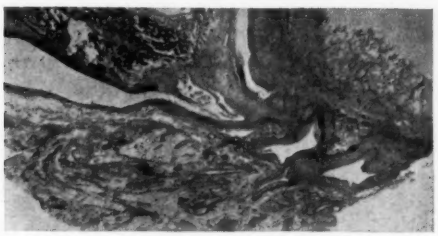

FIG. 3.—View of pedicle, showing tortuous tributary at base. Elastic and van Gieson: ×3·2.

Discussion

The osteogenic sarcomatous nature of the tumour was not realized at the time of the post-mortem examination, and an extensive examination of the bones was not carried out. Nothing suspicious was found in those bones examined, however, and the patient had no bone symptoms during life. The pulmonary vein is a highly unlikely site for a metastasis, and where there was slight penetration through the wall into the surrounding lung tissue, the appearances did not suggest that the vein had been invaded from without. The very structure of the tumour in fact suggests that it had originally been a benign polyp containing bone tissue which underwent malignant change.

Multiple ossifying cartilaginous nodules attached by fibrous pedicles within the left ventricles of rats were described by Farris *et al.* (1946). Bone marrow was found in some of them. The authors assumed that the changes were due to the metaplasia of fibroblasts in areas of degeneration or scarring from an unknown cause. It is possible that the lesions were congenital. Prichard (1951) suggested that myxomata of the left atrium arose from small malformations in the region of the fossa ovalis. These malformations consisted of excess fibrous tissue and in some cases minute areas where there were lacunæ of capillary size lined by plump endothelial cells. This suggestion has been supported by Raeburn (1952) who draws a comparison with epidermal moles. Myxomata sometimes contain bone. One of Prichard's cases had at its base large thick-walled blood vessels arising from deep within the atrial wall. Giaccai supported the theory of dysontogenetic neoplasia for some blood vessel tumours, particularly those arising from the pulmonary vessels, as they are in a zone where evolutive errors can occur frequently.

In our case the pedicle was situated where the pulmonary vein received an abnormal tributary, and we suggest that this patient had a small bone-containing hamartoma which eventually became malignant just as a skin nævus may become a malignant melanoma. The plasticity of mesenchymal tissue and its potency for aberrant differentiation is now generally acknowledged (Forbes, 1955).

Summary

A case is described of ball-valve obstruction of the mitral orifice by an osteogenic sarcoma of a pulmonary vein. The tumour was probably derived from a pre-existing hamartomatous polyp.

Our thanks are due to Mr. J. E. Wilson for access to the case records, to Mr. J. Teal for technical assistance, and to Dr. G. H. O. Burgess and Mr. H. Warley for the photographs.

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KAPOSI'S HÆMANGIOSARCOMA OF THE HEART

BY

MICHAEL GELFAND

From the African Hospital, Salisbury, Rhodesia

There are numerous reports of the frequency with which Kaposi's sarcoma is encountered in the African. It is a true but atypical sarcoma, starting as a single reddish or purplish nodule on one or both lower extremities. Further nodules form slowly and spread up the limb, while at the same time the earlier lesions tend to coalesce. The condition is generally bilateral, resulting in a stocking distribution, which later spreads to the trunk, upper limbs, or viscera. The African appears to possess a peculiar predisposition to the disease, which in Europe is frequent amongst the labouring classes in Italy, where it was originally described. Women are rarely affected. Death is invariable, but the interval between the onset of the condition and death varies. Visceral manifestations usually occur from two to five years after the onset of the disease, which generally terminates fatally in three to eight years.

Referring to the site of secondary deposits, Choisser and Ramsey (1939) include the respiratory tract, lymph nodes, stomach, intestines, liver, kidney, and bladder. In their review on the disease, they failed to find a case of cardiac or pericardial involvement, but were themselves able to record two European cases in which the lesions were primarily in the heart but not found in the skin: in both the disease ran a rapid downhill course, the patients dying of cardiac tymponade. Autopsy showed proliferative lesions, involving primarily the right atrum with spread to the myocardium, pericardium, diaphragm, and mediastinum, and isolated lesions in the liver and lungs. A closer study of reported cases revealed eight heart tumours variously diagnosed, in which they regarded the microscopical picture as identical with Kaposi's sarcoma although, as they stated in their review of cases reported as such, they had been unable to find a single instance in which the condition was primary in the heart.

The pathology of the disease is of interest. The tumour is composed of small newly formed blood vessels, with walls composed only of cells resting on a reticular base. In other places the blood sinuses are full of blood or debris. Small foci of polymorphonuclear leucocytes and lymphocytic infiltration are usually also present. As well as the blood vessels there are more solid portions of the tumour consisting of proliferative embryonic spindle cells differing in size, shape, and arrangement: some are small, others large, and all possess hyperchromatic nuclei with only an occasional mitotic figure. The structure of the tumour varies in different portions as does the pleomorphism in individual regions, but the important feature to be noticed is its vascularity.

Case Report

The patient was a well-built adult African male, aged about 38 years, who was admitted to the Salisbury Native Hospital. He complained that his feet and later his legs had begun to swell four months before and had become progressively worse until the time of his admission when it reached well up his trunk and included his arms. He had noticed too that he was short of breath on exertion, but did not experience any pain in the chest.

On examination, the patient was orthopnœic and œdematous. He was afebrile with a regular pulse and a blood pressure of 165/125. The veins in the neck were full and distended but did not pulsate. The apex beat could neither be seen nor felt and the heart sounds were distant and muffled. The left base on percussion was stony dull with absent air entry. An X-ray of the chest revealed an enlarged cardiac silhouette resembling a moderately large pericardial effusion and a moderate left-sided pleural effusion. The cardiogram showed very low voltage R and absent T waves in the

standard leads. The hæmoglobin was 107 per cent and blood urea 24 mg. per 100 ml. The total serum proteins were 6·5 g. per 100 ml. and the white cell count normal. The Wassermann reaction of the blood was negative.

The legs and feet were œdematous and showed no other abnormality save the skin over the extremities which was pellagroid in type. The liver was enlarged and its edge could be felt four fingers below the right costal margin, its edge and surface being smooth and hard. A moderate ascites was present.

A pericardial aspiration was performed and the clear straw-coloured fluid removed proved sterile on culture. As tuberculosis is the most common cause of pericardial effusion in the African, it was decided to institute a course of streptomycin. However, the patient failed to improve and died three weeks later.

Autopsy. At autopsy the significant changes were present in the heart which was enclosed in a clear straw-coloured pericardial effusion. On inspection the striking feature was that its whole surface (ventricles and atria) was covered in raspberry-like tumours of varying size (Fig. 1). The

FIG. 1

tumours were irregular in shape, some measuring as much as 18 mm. in length while others were much smaller, about 6 mm. They were studded over the whole myocardium, equally in each chamber, and had invaded the muscle to about a quarter of its depth. None could be seen on the endocardial surfaces and the valves were normal. The lungs and pleuræ were unaffected by these tumours in spite of the effusion in the left pleural sac and no growths were found anywhere else in the body. The liver was enlarged and congested. I did not recognize the nature of the disorder. Portions of the heart and tumours were submitted to Dr. J. F. Murray of Johannesburg who identified the condition as a *Kaposi hæmangiosarcoma*.

"The sections from the heart are most interesting. They show the presence of a Kaposi hæmangiosarcoma, a condition in which I have been interested for some years. During that time I have collected just over one hundred cases, but this is only the second in which cardiac lesions have been present."

The histological picture varied in the different parts of tissue examined. The disordered architectural arrangement and multiplicity of cellular proliferation were striking, with vascularity the common feature. In some parts the cells were spindle-shaped with little pleomorphism and with dark-staining nuclei. Between the cellular structure lay newly formed blood vessels consisting of endothelium and resting on a reticular base. These walls were at times broken, permitting extravazation of blood and their vessels were engorged with blood cells. In many respects this tissue might be mistaken for a soft fibroma or even chronic granulation tissue.

In other parts the structure was different with more primitive cells of varying size, shape, and arrangement, and a few mitotic figures. The nuclei were larger and stained pale blue. Some of the cells were arranged to form new blood vessels, sometimes in double layers and sometimes lining only a single layer. Sheets of these cells invaded the myocardium often at some distance from the main site of the tumour.

Comments

There were two points of special interest in this case. First, the clinical picture was that of a pericardial effusion believed to be tuberculous. Secondly, no lesions of Kaposi's tumour were present in the skin or internal organs other than the heart. Although Kaposi's tumour, as a cause of heart failure, is uncommon, it should be remembered as a possibility in a male African when the ætiology is not immediately obvious.

I wish to thank Dr. R. M. Morris, Secretary for Health, Rhodesia and Nyasaland for his permission to publish this paper.

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REPETITIVE PAROXYSMAL VENTRICULAR TACHYCARDIA WITH FUSION BEATS

BY

RUSTOM JAL VAKIL

From the Cardiological Department, King Edward Memorial Hospital, Bombay

Paroxysmal ventricular tachycardia is unfortunately fairly common and is usually associated with serious heart disease and a poor prognosis. Of late, however, attention has been drawn by numerous observers to a rare and apparently benign form where paroxysms of ventricular tachycardia interrupted by normal sinus beats keep on recurring for months or years.

In view of the apparent rarity of the repetitive form of paroxysmal ventricular tachycardia and the presence of some unusual features the following case is reported.

Case Record

A Hindoo shopkeeper, aged 38 years, was investigated for vague attacks of palpitation accompanied by sweating. Until the age of 36, he had always been well, and had indulged in strenuous physical exercise. In early 1954, for no apparent reason he started having momentary attacks of irregular or fast beating of the heart accompanied by sweating but no pain or dyspnœa. These attacks were extremely variable in intensity, duration, and frequency, sometimes occurring as often as " several hundred times a day," sometimes only once or twice in the day. They seemed more frequent after physical effort. In spite of and even during the attacks, he had continued working at his job and indulged in moderate exertion.

On examination, he was a thin man of average height and good colour. Apart from irregular beating of the heart, the cardiovascular system was normal, both clinically and fluoroscopically; the blood pressure was 120/84. The Wassermann and Kahn reactions were negative and the blood count and urine and the other systems were normal.

Electrocardiograms (Fig. 1) taken on several occasions revealed characteristic paroxysms of ventricular tachycardia of variable length interrupted by one or more normal sinus beats. They were sometimes preceded by ventricular fusion beats (marked F in the Fig.) and were followed by long pauses.

With the oral administration of quinidine sulphate, 0·2 g. four times daily for twelve days, the paroxysms were controlled and the patient became free of all symptoms. Throughout the entire period of illness, he had not become incapacitated.

Discussion

The repetitive form of paroxysmal ventricular tachycardia, although variously referred to in the past (Gallavardin, 1922; Gallavardin and Dumas, 1924; Cassidy, 1924; and Froment, 1932), is perhaps best described by the term repetitive paroxysmal tachycardia recommended by Parkinson and Papp (1947).

The first case of repetitive paroxysmal tachycardia of auricular type was reported by Lewis in 1909 when, with the aid of the polygraph, he recorded 54 paroxysms of auricular tachycardia within 109 minutes in a healthy man. The ventricular variety was reported independently, for the first time by Gallavardin in France and by Scott in England in 1922. Since then, over thirty cases of this type have been reported by numerous observers, and the subject has been reviewed by Parkinson and Papp (1947).

The favourable outlook of repetitive paroxysmal tachycardia has been the subject of comment (Routier, 1937; Campbell and Elliott, 1939; Miller and Perelman, 1945; and Parkinson and Papp,

1947). One of the striking features of the present case was the amazing tolerance displayed by the patient towards the disability even while experiencing several hundred paroxysms of tachycardia a day.

The characteristic feature was runs of paroxysms of bizarre ventricular complexes separated by one or more normal sinus beats (Fig. 1). The possibility of supraventricular tachycardia with

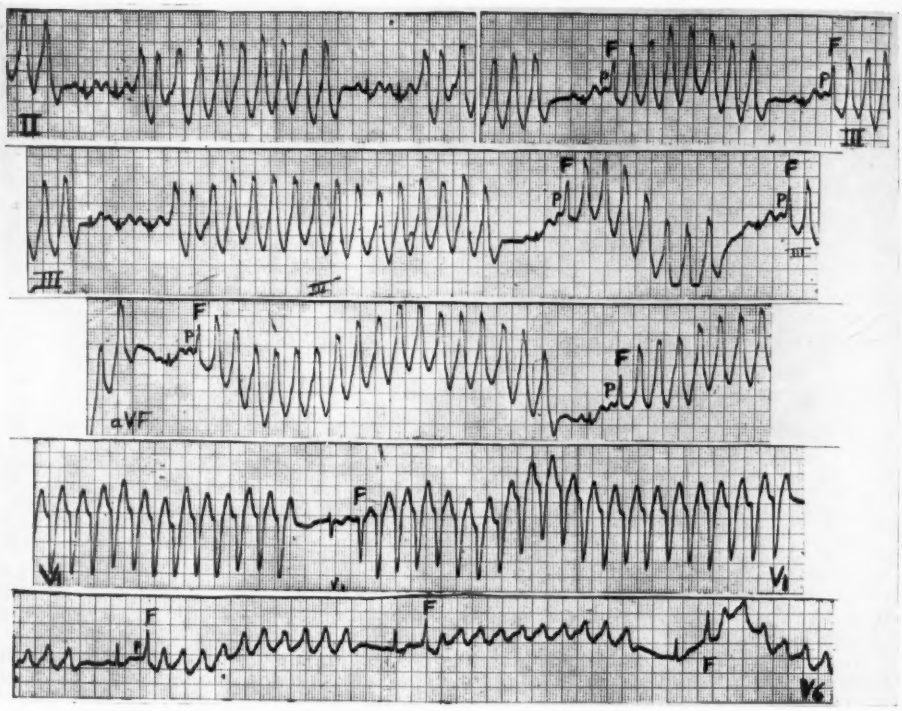

FIG. 1.—Runs of repetitive ventricular paroxysmal tachycardia, interrupted by normal sinus beats. Fusion beats (F) were noted at the onset of some of the paroxysms. The ectopic ventricular beats with bizarre complexes show variations of contour and spacing, the rate ranging between 264 and 214 a minute. The termination of each paroxysm is followed by a characteristic pause. Sinus P waves are difficult to detect during the paroxysms.

aberrant conduction within the ventricles, which has been shown to mimic genuine ventricular tachycardia (Lewis and Master, 1925–26; Gouaux and Ashman, 1947; and Katz and Pick, 1956) was considered in the present case but rejected in view of (1) the variability in the rate of ventricular beating (from 264 to 214 a minute) during paroxysms, (2) the long pause subsequent to each paroxysm, and (3) the somewhat characteristic configuration of the QRST complexes. The condition was therefore regarded as one of paroxysmal ventricular tachycardia of repetitive type.

Another feature of interest was the atypical complex marked F in Fig. 1. Although most paroxysms of tachycardia were preceded by normal sinus beats, an atypical complex marked F was found to precede the initial beat of the paroxysm in a fair proportion. In view of the upright P wave, shortened P–R interval, and QRS configuration intermediate between that of the normal sinus beat and of the bizarre complex of the paroxysm, the F beat was regarded as an example of a fusion beat (Malinow and Langendorf, 1948) resulting from the fusion of a supraventricular with a ventricular impulse. As far as can be ascertained, this is probably the first case of its kind where

a fusion beat has been reported in conjunction with repetitive paroxysmal ventricular tachycardia associated with normal sinus rhythm.

Summary

Repetitive paroxysmal tachycardia of ventricular type is reported in a man of 38 years. Amongst the noteworthy features about the case were (1) the tolerance of the patient towards the disability, and (2) the presence of fusion beats of ventricular type at the onset of many of the paroxysms.

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DUPLICATION OF THE MITRAL VALVE

BY

E. D. WIGLE*

From the Department of Pathology, Postgraduate Medical School, Hammersmith

Duplication of the mitral valve is a rare congenital cardiac anomaly, only twenty instances having been previously reported. There are on record in addition two cases of triplication of the mitral valve, a condition presumably resulting from a similar defect in development. Duplication of the tricuspid valve also occurs, but less commonly than the mitral anomaly. This case is reported in order to draw attention to several interesting facets of the condition, namely, the embryology, the occasional presence of an apical diastolic murmur, and the association with certain other congenital cardiac anomalies.

Case Report

Present Illness. On August 10, 1955, a sixty-five-year-old single woman was admitted for the first time to Hammersmith Hospital with a history of having had attacks of winter bronchitis for the past twenty years, ankle œdema for eighteen months, and a severe attack of bronchitis six months previously. The latter was followed by progressive loss of weight, exertional dyspnœa, orthopnœa, and angina pectoris. For the three weeks prior to admission the patient noted extreme weakness and pleuritic pain on the right side of the chest.

Past History. The patient spent a normal active childhood, although she was told when very young that she had a damaged heart valve. Hysterectomy was performed for adenocarcinoma of the body of the uterus in 1948; the blood pressure was then 195/115. Between 1951 and 1954 she was operated on for partial thyroidectomy and intestinal obstruction. While in hospital she was found to have aortic and mitral valve disease.

Examination revealed a pale, febrile, seriously ill woman. The heart was enlarged to the left. There was an aortic systolic murmur and thrill, an apical mid-diastolic murmur, a loud pericardial friction rub, and evidence of moderately severe congestive cardiac failure. Blood pressure: 120/75. Investigation revealed a severe iron deficiency anæmia and occult blood in the stools. Serial electrocardiograms revealed right and left ventricular hypertrophy, pericarditis, and possible antero-septal ischæmia. Fluoroscopy of the chest showed enlargement of the left atrium, and of the left and right ventricles. A barium meal demonstrated a mass pressing on the greater curvature of the stomach. There was no laboratory or clinical evidence to suggest a diagnosis of myxœdema.

During the patient's stay in hospital the congestive heart failure responded well to digitalis and mercurial diuretics, but she remained febrile and very weak. Repeated blood transfusions corrected the anæmia and improved her general condition to some extent. On October 31 the patient developed severe pain in the left hypochondrium and a large craggy mass then became palpable in this region. Following this, her condition deteriorated gradually and two weeks later the abdomen became distended and the size of the mass in the left hypochondrium increased. Operation was considered, but the patient's general condition forbade this, and she died four days later.

Post-mortem Examination (7403)

This was performed 36 hours after death. In the lungs there was evidence of chronic bronchitis, bilateral pulmonary œdema, and basal bronchopneumonia, and congenital absence of the right middle lobe. There was a volvulus of the terminal portion of the ileum causing incomplete obstruction, resulting in dilatation

* During the tenure of a British Council Scholarship.

of the small intestine proximally. The spleen was massively enlarged, measuring 28 × 15 × 15 cm., all but the tip being replaced by necrotic tumour tissue (primary in uterus, 1948). The interval between removal of the primary site and the recurrence of secondaries was long (8 years), but not exceptionally so (Willis, 1952). One gland at the hilum of the spleen was also involved by tumour. There was a medullary fibroma of the right kidney.

Examination of the Heart and Great Vessels. There was coarctation of the aorta of adult type, the lumen at the point of narrowing measuring 15 mm. in diameter. There was dilatation of the ascending aorta, aneurysmal dilatation of the proximal 3 cm. of the left subclavian artery and a patch of atheroma on the medial wall of the aorta immediately distal to the coarctation. No evidence of collateral circulation was found. The heart weighed 499 grammes and the epicardial surface showed evidence of fibrinous pericarditis. The left and right ventricles were hypertrophied, their outflow tracts measuring 21 and 5 mm. in thickness respectively. There was also hypertrophy and slight dilatation of the left atrium. The aortic valve was bicuspid, the cusps being of equal size. The two coronary arteries, which were free of atheroma, arose from the two extremes of the anterior cusp. The cusp margins were thickened and rolled, but not appreciably retracted. The aortic orifice would admit the tip of an index finger. There was a calcified median raphe of the anterior cusp that did not extend to the free margin. Masses of calcium were present in the sinuses of Valsalva and on the ventricular surface of the posterior cusp. From the latter area a ridge of calcium extended down on the ventricular surface of the anterior mitral cusp to its free margin, limiting normal movement of this leaflet (Fig. 1). The mitral valve itself was duplicated (Fig. 1 and 2), the anterior and posterior orifices measuring 40 and 60 mm. in circumference respectively. These orifices were separated by a bridge of fibrous tissue 9 × 3 mm. to which chordæ tendineæ were attached. This bridge appeared to be dividing what was otherwise a normal mitral valve. Each orifice had two cusps of

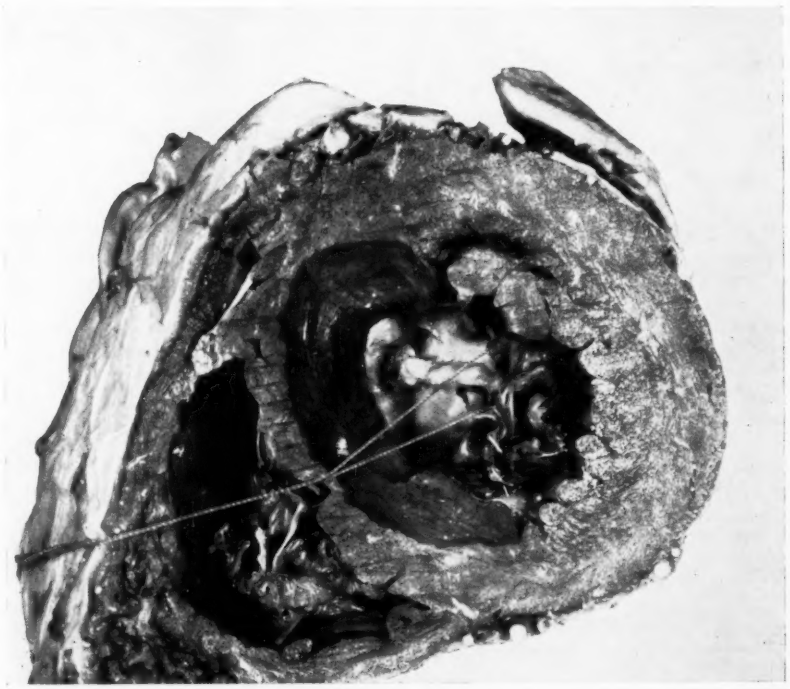

FIG. 1.—Duplication of the mitral valve viewed from the left ventricle. A piece of thread has been looped under the fibrous "bridge" to hold the valve cusps apart. Note the ridge of calcium extending down from the posterior cusp of the aortic valve.

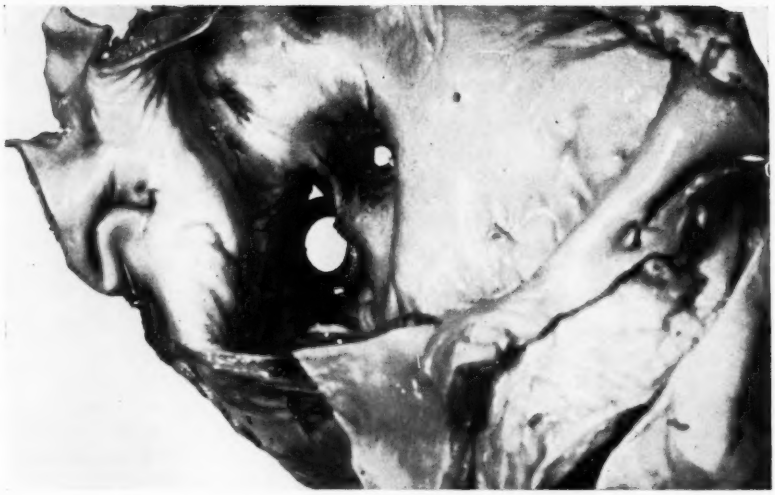

FIG. 2.—Duplication of the mitral valve viewed from the left atrium. Pieces of rubber have been inserted into the orifices of the formalinized specimen to hold them open. The smaller anterior orifice is slightly to the left of the posterior orifice.

normal appearance. The chordæ tendineæ to the cusps of the anterior orifice arose from a small group of papillary muscles high on the anterior wall of the left ventricle. The chordæ to the posterior orifice arose from a larger anterior papillary muscle and the posterior papillary muscle. No evidence of previous rheumatic disease was found either in the gross or in the microscopic examination of the heart.

Discussion

In eight of the twenty cases of duplication of the mitral valve hitherto reported, the two orifices were of equal size. Of the twelve cases with unequal sized orifices, the smaller " accessory " orifice was anterior in ten and posterior in two. In seven of the ten cases with a smaller anterior orifice, this orifice was described as being a hole in the anterior mitral cusp; in one of the two cases with a smaller posterior orifice, the accessory orifice was described as being a hole in the posterior cusp. In the remaining four cases with unequal orifices and in the eight cases with equal sized orifices, the authors described the valve as being divided by a " bridge " of fibrous tissue.

Sixteen of the cases were described as having two normal cusps for each orifice; in the remaining four cases the cusps of the smaller orifice were described as being rudimentary or absent. In ten of the twelve cases with adequate descriptions of the papillary muscles, the chordæ tendineæ from the anterior papillary muscle were attached to the cusps of the anterior orifice and the chordæ from the posterior papillary muscle were attached to the cusps of the posterior orifice. In Cohn's case (1897) and that of Davies and Fisher (1934), an anterior papillary muscle supplied chordæ to the anterior orifice and a second anterior papillary muscle plus the posterior papillary muscle supplied chordæ to the posterior orifice. Of the fourteen cases in which the sex of the subject was mentioned nine were male and five female.

In all but three cases the duplicated mitral valve was an incidental post-mortem finding. In the case described by Davies and Fisher, an apical mid-diastolic or presystolic murmur was heard from time to time over a number of years of observation. Their patient had in addition coarctation of the aorta and a bicuspid aortic valve. Matterstock's (1877) case had an apical diastolic murmur for the three days prior to death, the patient dying of a severe anæmia. The physician who discussed Paul's (1930) case stated that there was evidence of mitral stenosis and insufficiency, plus a diastolic murmur at the point of Erb; in this patient there was in addition subaortic stenosis, a bicuspid aortic valve, and a patent ductus arteriosus.

Associated congenital cardiac anomalies were noted in six of the twenty cases, the commonest of these being a bicuspid aortic valve (three cases) and a persistent ostium primum (three cases).

Embryology. Though Camisa (1912) believed his two cases to be due to fœtal endocarditis, the developmental basis for duplication of the mitral valve now seems well established. Normally in early embryonic life, the ventral and dorsal endocardial cushions of the primitive atrio-ventricular canal fuse, thereby forming the left and right primitive atrio-ventricular openings (Fig. 3, I and II). The left segments of the fused ventral and dorsal endocardial cushions form the medial cushion of the mitral orifice and project into the left ventricle as the ventral and dorsal tubercles of that cushion. Subsequently the lateral mitral cushion is formed, and, by an undermining process, these cushions are converted into the medial (anterior) and lateral (posterior) mitral cusps.

In 1948 Wimsatt and Lewis described two different embryological theories to explain duplication of the mitral valve. Wimsatt believed, as did Hartmann (1937), that the anomaly was due to adhesion between the ventral or dorsal tubercles of the medial cushion with the lateral cushion (Fig. 3, III). Adhesion between the ventral tubercle and the lateral cushion would give rise to a smaller anterior orifice and adhesion between the dorsal tubercle and the lateral cushion would give rise to a smaller posterior orifice. Two orifices of equal size would result from fusion near the mid-point of each cushion. Wimsatt believed that with growth of the left ventricle the point of fusion would be subjected to tension and drawn out to form the bridge of fibrous tissue described in so many cases.

Lewis, on the other hand, believed that duplication of the mitral valve resulted from failure of complete

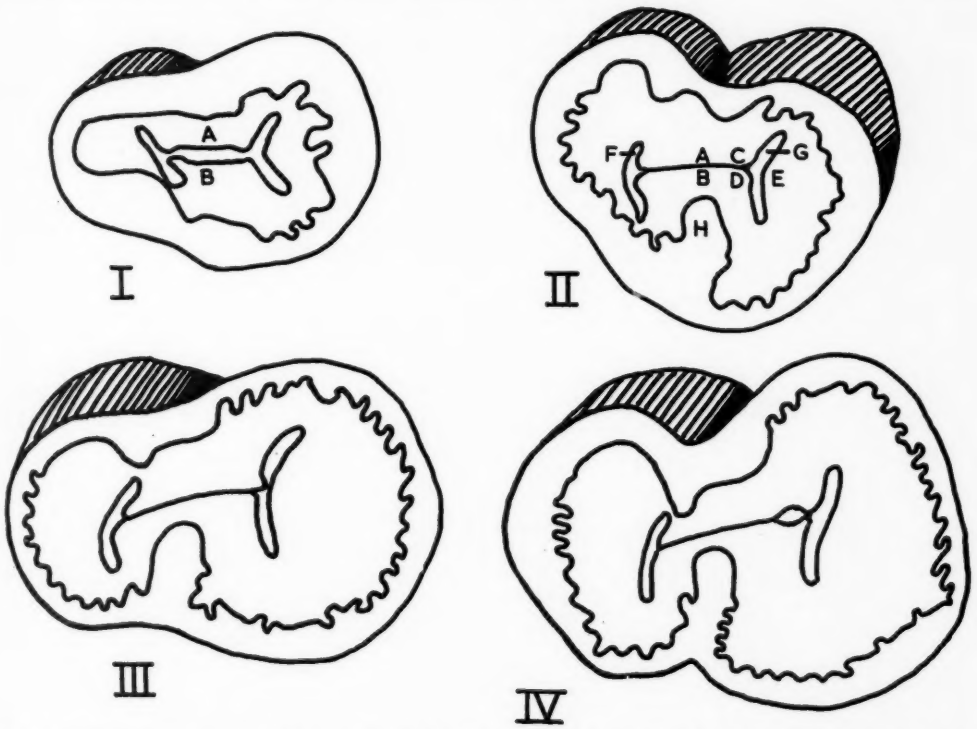

FIG. 3.—The diagrams represent embryonic hearts in which the apex has been cut off and the specimens viewed from below. I and II show the normal development of the mitral valve before, and after, fusion of the ventral and dorsal endocardial cushions. III shows the fusion of the ventral tubercle of the medial mitral cushion with the lateral cushion (Wimsatt). IV shows the failure of complete fusion of the left segments of the ventral and dorsal endocardial cushions (Lewis).

A, Ventral endocardial cushion; B, dorsal endocardial cushion; C, ventral tubercle of the medial cushion; D, dorsal tubercle of the medial cushion; E, lateral cushion; F, right A.V. orifice; G, left A.V. orifice; H, interventricular septum.

fusion of the left segments of the ventral and dorsal endocardial cushions medial to the tubercles (Fig. 3, IV). The accessory orifice thus represented a remnant of the primitive atrio-ventricular canal. He pointed out that this theory would explain the fact that in many cases the accessory orifice was described as a hole in the anterior cusp of the valve.

In the present case the fibrous bridge appeared to be dividing what was otherwise a normal mitral valve. This fact would seem to favour the adhesion theory of Wimsatt and Hartmann as the mode of evolution of the double mitral valve in this instance.

Of considerable interest in this case is the fact that the patient was diagnosed in life as having mitral stenosis, on the basis of the apical mid-diastolic murmur heard by numerous observers over a period of at least four years. As noted above, a similar murmur was heard repeatedly in two other cases of duplication of the mitral valve and terminally in a third case. Thus, it seems evident that duplication of the mitral valve may occasionally mimic mitral stenosis. Furthermore, in Davies and Fisher's patient and in the present case, coarctation of the aorta was present in addition to the double mitral valve and in both an apical diastolic murmur was noted. Wood (1950) and Cleland *et al.* (in press) have drawn attention to the apical mid-diastolic murmur often heard in cases of coarctation of the aorta. In the series of Cleland *et al.*, fifteen of the forty cases were noted to have an apical diastolic murmur prior to resection of the coarctation, and in nine of these the murmur was still present after operation. It is perhaps possible that duplication of the mitral valve might account for the murmur in some of the cases of this latter group, since the mitral anomaly and coarctation can occur in the same person.

In seeking the reason for the mitral murmur in this case, it is interesting to note that though the total circumference of the two orifices was 100 mm. (the normal circumference of the mitral valve being 90 to 110 mm.) the total area of the two openings (415 sq. mm.) was approximately one-half that of a normal mitral valve (800 sq. mm.). Thus, there was present a form of congenital mitral stenosis. Other possible causes of this murmur could have been an eddying of blood about the fibrous bridge, or even a relative obstruction to blood flow by the anterior mitral cusp which was rendered semi-rigid by the calcium present.

A further point of interest in this case is the development of calcific aortic stenosis upon a congenital bicuspid aortic valve that is associated with coarctation of the aorta. Smith and Matthews (1955) have drawn attention to this occurrence and they concluded that the stenosis results from degenerative changes in the abnormal valve, which is subjected to high pressures as a result of the co-existing coarctation.

Summary

A 65-year-old woman, who presented with signs of congestive cardiac failure, had clinical evidence of both mitral and aortic stenosis. At necropsy she was discovered to have duplication of the mitral valve, a bicuspid aortic valve with superimposed calcareous stenosis, and mild coarctation of the aorta.

I am very grateful to Professor C. V. Harrison for his advice and help in the preparation of this report and to Doctor C. L. Cope for permission to study the case record. My thanks are also due to Miss R. Klein for the photographs and to Mr. F. G. Saunders for the diagrams.

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INCREASED CARDIAC OUTPUT CAUSED BY SECONDARY HYPERNEPHROMA

BY

GEOFFREY BOURNE

From St. Bartholomew's Hospital, London

The local vascularity occurring in some cases of Paget's disease is sufficient to establish what amounts to an arterio-venous shunt that is large enough to lower the diastolic blood pressure and to increase the left ventricular output (Edholm *et al.*, 1945, and McMichael, 1947). The present case is that of a man, aged 72, in whom a secondary hypernephroma in the left tibia produced similar conditions.

When first examined his chief complaints were increased shortness of breath on exertion, cough, lassitude, and pain in the left shin. He had also considerable orthopnœa and was sleeping badly. He gave a history of having had a nephrectomy six years previously for hypernephroma. On examination he was very short of breath undressing, and was orthopnœic. The heart rate was 100, the rhythm was regular. There was a large pulse pressure (180/80). The heart sounds were normal. The electrocardiogram showed right bundle-branch block. There were signs of collapse and of impaired respiratory function over the right lower lobe. Pitting œdema was present over both lower legs. The hæmoglobin was 102 per cent.

The left tibia in its upper quarter was the site of a large, fairly firm, warm swelling (Fig. 1) measuring 7·5 by 5·0 cm. Over the whole of this swelling expansile pulsation was felt, and a prolonged musical systolic murmur was heard. X-ray screening of the chest showed a large mass in the right lower quadrant almost certainly caused by a secondary deposit. There appeared to be a small quantity of fluid in the right pleural cavity. The radiological report was as follows: in the right lung, there was a massive opacity projecting out from the region of the right hilum, and some dense punctate shadows in the lower zone with right basal pleural effusion; the left lung was clear except for a few scars.

There was extensive bone erosion in the upper third of the left tibia anteriorly, with some swelling of the soft parts. Some alteration of the trabecular structure nearby indicated associated Paget's disease: these latter changes were slight and local, those due to the secondary deposits greatly predominating. In the upper third of the right tibia there were poorly demarcated areas of erosion and a more sharply demarcated area of bone erosion in the lower third with some cortical bone expansion.

He was thought to have a neoplasm in the region of the right hilum with pleural effusion. The tibial bone lesions were thought to be secondary deposits. There was no evidence of secondary deposits or of Paget's disease in the dorsal or lumbar spine, in the pelvis, or in the long bones.

When massive vascular secondary deposits occur in the sternum or ribs the presence over them of a systolic thrill and a systolic murmur, and the fact that they may manifest expansile pulsation, can cause them to mimic very closely aneurysms of the aorta (Dr. R. Bodley Scott, personal communication).

The patient was admitted to St. Bartholomew's Hospital for further investigation and for deep X-ray treatment of the secondary deposit in his left tibia, which was causing him much pain and disability. The investigations that are the subject of this communication were concerned with the secondary tumour in the left tibia. A *phonocardiogram* (Fig. 2) taken by Dr. B. G. Wells showed that the murmur in the tibia was continuous, and that it had the characteristics of the murmur of an arterio-venous fistula, being maximal at the time of the second heart sound.

Peripheral Blood Flow. Investigations on the peripheral blood flow were performed by Dr. Robert Duff. Under standard conditions (room temperature 23·0° C.; plethysmograph temperature 35·0° C.) blood flow was measured in the feet

FIG. 1.—The swelling caused by the secondary hypernephroma in the upper part of the left tibia. The dark lines are guides for deep X-ray therapy.

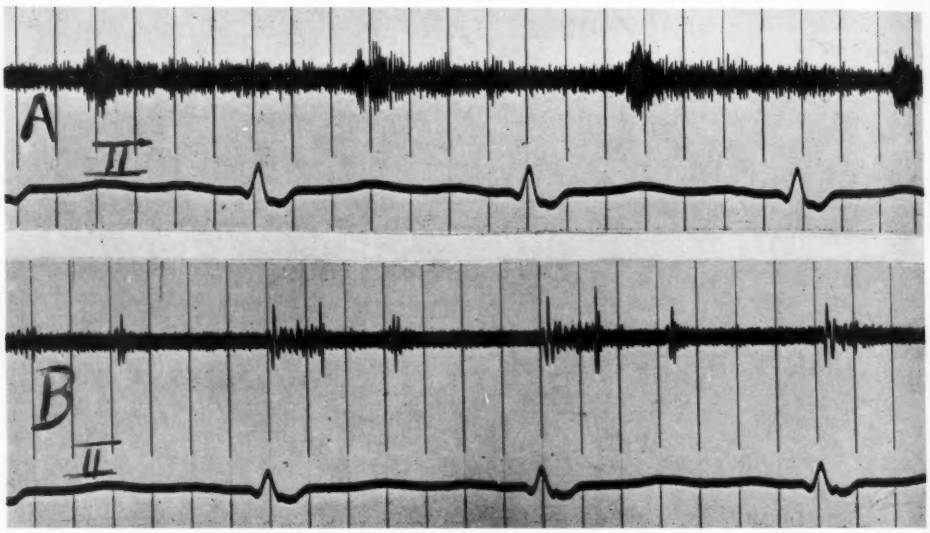

FIG. 2.—Phonocardiogram with electrocardiogram (lead II). (A) Over the left leg below the knee. (B) At the apex. The heart sounds are normal and the systolic sound is inconstant and may be due to improper sealing of the bell chestpiece. The murmur in the leg is continuous and has the characteristics of the murmur of an arterio-venous fistula, being maximal at the time of the second heart sound.

by venous occlusion plethysmography. The blood flow in both feet ranged between 8 and 10 ml./100 ml. of foot volume/min., there being no significant difference between the two sides. It was possible to measure the blood flow under similar conditions in the left knee, a plethysmograph being placed so as to enclose the knee joint and patella and the upper end of the tibia including the metastatic swelling. The flow through these ranged from 15·0 to 27·0 ml./100 ml. tissue volume/min. with an average of 21 ml.

The flow in the feet was high, though not outside the upper range of normal, but was not significantly greater in the left foot. In the left knee, a very high value was recorded; although comparable measurements in healthy subjects are not available there is no doubt that this represents a pathological increase, for the blood flow in the knee should be no greater than that in the foot, under these standard conditions.

Left Femoral Artery Occlusion by Digital Pressure. The diastolic pressure during the control period ranged from 70 to 76 with a mean value of 74 mm. Hg. On occluding the left femoral artery it rose immediately to 80 mm., then fell to 76, and rose once more to 78 at which point it was maintained during the minute that the artery was occluded. On release of the femoral artery, the diastolic blood pressure fell after a few seconds to 74 mm. at which level it was maintained steadily to the completion of the observation. The rise in diastolic blood pressure, though small, was constant and presumably signified that a large volume of blood was shunting from the arterial to the venous circulations in the left lower extremity. Digital occlusion of the left femoral artery was attended by an immediate fall in the heart rate from 98 to 92 a minute—further evidence that the shunt in the left lower extremity was considerable.

Finally, an angiogram on the local vascular condition by Mr. G. W. Taylor showed the presence of sizeable arterial circulation round the upper end of the left tibia.

When the patient was re-examined three months after deep X-ray treatment the shin swelling was much reduced in size, the systolic thrill and murmur had disappeared, and the pulse pressure was no longer increased (140/70).

Conclusion. It is clear from these observations that a massive vascular secondary deposit in bone can produce changes in the circulation similar to those caused by the vascular stages of Paget's disease.

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AUSCULTATORY AND PHONOCARDIOGRAPHIC SIGNS OF PULMONARY STENOSIS

BY

AUBREY LEATHAM AND DAVID WEITZMAN

From the Institute of Cardiology, National Heart Hospital

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The course and management of pulmonary stenosis depends on two main factors, the degree of obstruction to right ventricular outflow and the presence and extent of an over-riding aorta with a ventricular septal defect. This investigation was undertaken to determine how accurately these points could be decided by study of the heart sounds and murmurs. The pulmonary systolic murmur has long been recognized as the most important sign (Peacock, 1866), but the significance of its duration and graphic form has not been widely appreciated. Little attention has been paid to the first heart sound since Petit in 1902 commented on its snapping quality at the base in some cases. The second heart sound at the pulmonary area has been variously described as accentuated, normal, diminished, or absent: this has been due to failure to differentiate between aortic and pulmonary components of the second sound at the pulmonary area as pointed out by Abrahams and Wood (1951). The present investigation shows that the presence or absence of the pulmonary component and its delay in relation to the aortic component are of considerable help in diagnosis.

METHOD

Seventy patients with pulmonary valvular or infundibular stenosis were studied. The clinical diagnosis was confirmed by cardiac catheterization or angiocardiography in all, and also by operation in thirty-five and by necropsy in three cases.

Auscultation was always carried out by one of us and the intensity of heart sounds and murmurs was graded, the classification of Freeman and Levine (1933) being used for systolic murmurs. Special attention was paid to the first and second heart sounds, and to the intensity and length of the systolic murmur. High-frequency phonocardiograms corresponding to auscultation (Leatham, 1952) were taken in every case, and were repeated in six after operation. Simultaneous recordings were made from the pulmonary and mitral areas together with an electrocardiogram and an indirect carotid pulse tracing in every case, and synchronously with a pressure pulse from the pulmonary artery and right ventricle in eleven cases. The mitral and tricuspid components of the first sound and the ejection sound were identified by methods already described (Leatham, 1954). The aortic component of the second sound was identified by its relation to the dicrotic notch of the carotid tracing allowing for a delay of from 0·02 to 0·04 second. The pulmonary component was identified by its maximum intensity at the pulmonary area and by its synchrony with the dicrotic notch of the tracing from the pulmonary artery when this was obtained simultaneously. The two components of the second heart sound were also identified by taking synchronous phonocardiograms from the pulmonary and mitral areas, since only the aortic component is transmitted to the apex (Leatham, 1954).

The duration of right ventricular systole was estimated by measuring the time interval between the tricuspid component of the first sound and the pulmonary component of the second. In the same way left ventricular systole was estimated, using the mitral and aortic components of these sounds. In many patients the first sound was single and both measurements were taken from the onset of the major deflections of the first sound. The time interval between the onset of QRS and the onset of right ventricular systole (Q–RV time) was measured in the 64 patients who were catheterized. Time intervals were measured from the onset of all deflections whether pressure pulse, electrocardiogram, or phonocardiogram.

A full electrocardiogram was always taken and the degree of right ventricular hypertrophy was estimated without knowledge of the right ventricular systolic pressure.

The patients fell into three groups each with distinctive clinical, auscultatory, phonocardiographic, and hæmodynamic findings.

(1) Mild pulmonary stenosis with intact ventricular septum (11 cases).
(2) Moderate or severe pulmonary stenosis with intact ventricular septum (33 cases).
(3) Fallot's tetralogy (26 cases).

Mild Pulmonary Stenosis

These patients had no significant symptoms and were often referred following mass X-ray examination which had disclosed dilatation of the pulmonary artery: none had any enlargement of the heart radiologically. Cyanosis and clubbing were absent and there was no clinical or electrocardiographic evidence of right ventricular hypertrophy. The right ventricular systolic pressure ranged from 15 to 40 mm. Hg, and there was a pressure gradient across the pulmonary valve of 6 to 26 mm. Hg. In no case was there evidence of an infundibular chamber or of a left-to-right shunt. These small pressure gradients might have been produced by dilatation of the pulmonary artery alone (Greene *et al.*, 1949) and we were unable to distinguish between this condition and mild pulmonary stenosis, especially as none of these patients came to operation or necropsy. Lack of

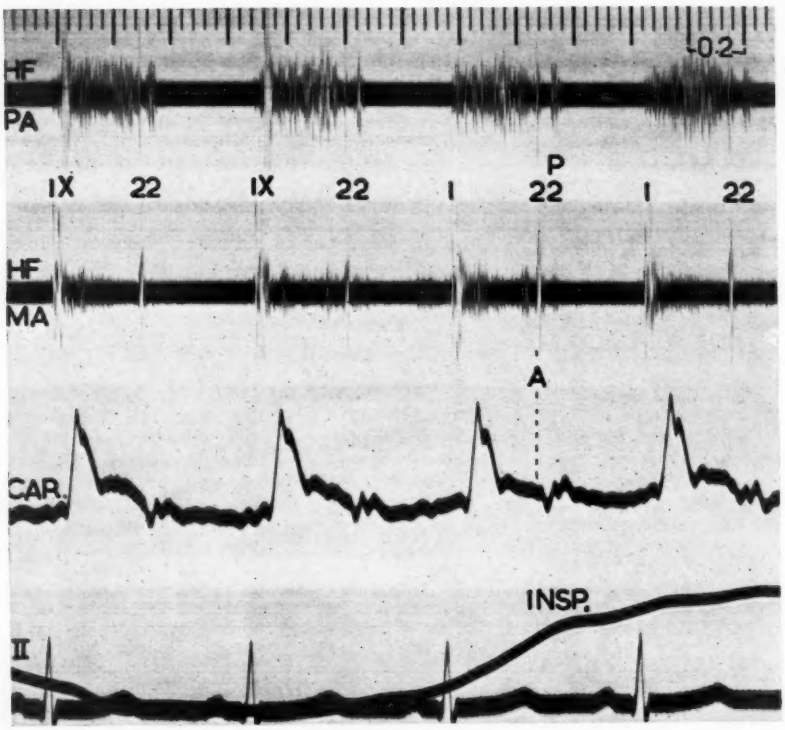


FIG. 1.—Mild pulmonary valve stenosis (RV P mean. 19 mm. Hg, PA P mean. 10 mm. Hg). Simultaneous high-frequency phonocardiograms (HF) from the pulmonary (PA) and mitral (MA) areas with indirect carotid tracing (CAR) and electrocardiogram. Pulmonary early systolic ejection sound (X) maximal at the pulmonary area and disappearing on inspiration (INSP). Splitting of second heart sound with aortic component (A, indentified by carotid tracing) preceding pulmonary component (P) by 0·05 sec. Ejection systolic murmur maximal at pulmonary area. The time intervals in this and subsequent records are 0·20 and 0·04 sec.

appreciable stenosis was demonstrated in one case by passing a double loop of the catheter through the valve. The dilatation of the main pulmonary artery seemed greater in this group than in the more severe cases, but the appearance of dilatation was perhaps exaggerated by absence of hypertrophy of the adjacent outflow tract of the right ventricle in mild cases.

The first sound was normal and was followed in every case by an extra sound at an interval of 0·02 to 0·06 sec. (mean 0·04). This gave the impression of wide splitting of the first heart sound, but the extra sound was clicking in quality, and maximal at the pulmonary area and in expiration (Fig. 1). These features are characteristic of a pulmonary ejection sound (Leatham and Vogelpoel, 1954) and in four cases we were able to confirm this by recording both mitral and tricuspid components of the first sound preceding the extra sound (Fig. 2). The exact relation of this sound to

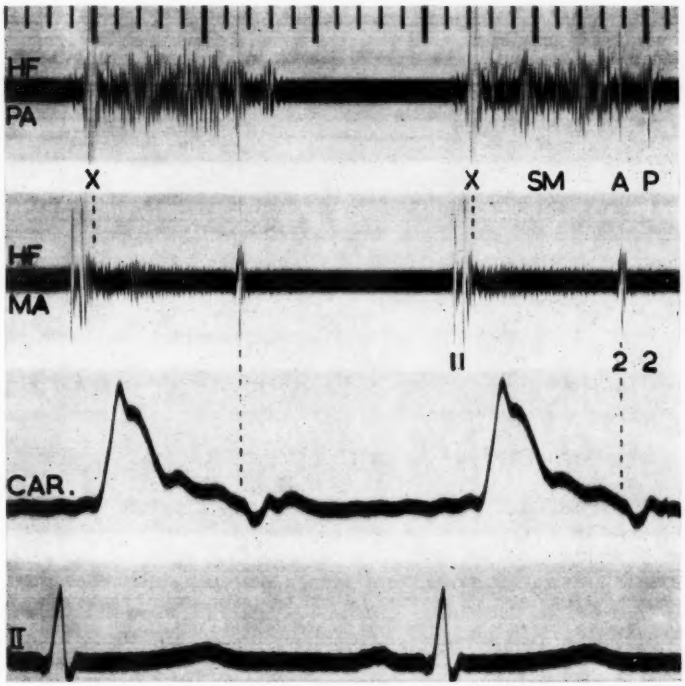


FIG. 2.—Mild pulmonary valve stenosis (same patient as Fig. 1). Both components of the first sound recorded at mitral area, preceding ejection sound at pulmonary area. Pulmonary component of second sound identified by its localization to pulmonary area.

the pulmonary artery pressure pulse could not be demonstrated because of the difficulty of obtaining good pressure records from the pulmonary artery in pulmonary stenosis, but it was shown to occur after the onset of rise of pressure in the right ventricle (Fig. 3).

In every case there was abnormally wide splitting of the second heart sound in the expiratory phase of respiration. The earlier component was shown to be due to aortic, and the later to pulmonary valve closure (Fig. 2 and 4), and the interval between the two components in expiration was 0·03–0·06 sec. (normal 0·01–0·03 sec.), increasing to 0·04–0·07 sec. during inspiration as in normal subjects. The intensity of the pulmonary component was judged to be normal by auscultation

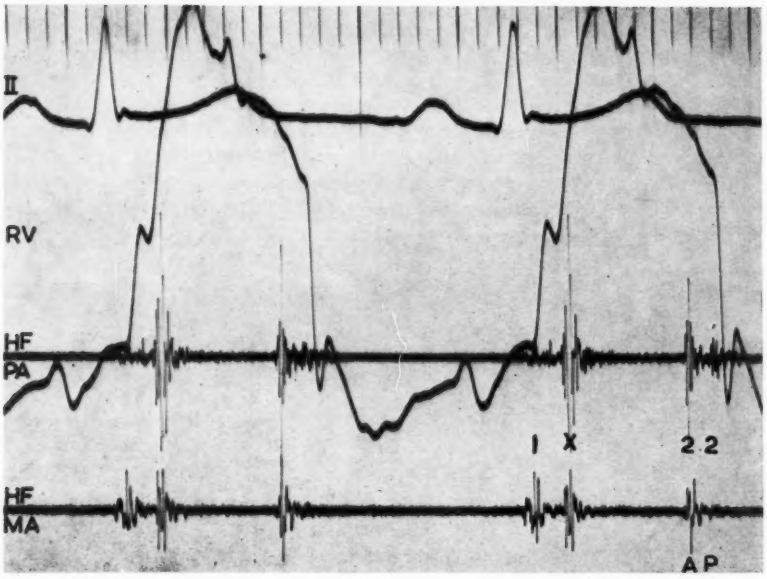


FIG. 3.—The relation of the right ventricular pressure pulse (RV) to the first heart sound and pulmonary early systolic sound in a patient with mild pulmonary valve stenosis. The major components of the first heart sound are approximately coincident with the rise of pressure in the right ventricle and the extra sound occurs 0·06 sec. later, showing that it has no connection with closing of the tricuspid valve.

and this was confirmed by the ratio of the amplitude of the two components of the second sound on the phonocardiogram. The pulmonary component was never less than one-third of the aortic and was about equal in four cases. There was invariably a systolic murmur maximal in the pulmonary area (Table, p. 307). The intensity of the murmur varied from soft (grade 1) to moderately loud (grade 3) and was increased by exertion. The murmur started immediately after the ejection sound, occupied early and mid systole, sometimes reaching the aortic component of the second sound, and finished before the pulmonary component. Pulmonary diastolic murmurs were never heard or recorded, showing that there was no pulmonary incompetence, even with great dilatation of the pulmonary artery.

MODERATE OR SEVERE PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM

All these patients had clinical and cardiographic evidence of right ventricular hypertrophy. Five showed cyanosis from a reversed inter-atrial shunt. The right ventricular systolic pressure ranged from 50 to 160 mm. Hg. The stenosis appeared to be valvular in 29 cases (confirmed by operation or necropsy in 15), infundibular in 4, and both valvular and infundibular in one (necropsy confirmation). This group corresponds to those with normal aortic root described by Abrahams and Wood (1951).

The first sound was normal and was preceded by an auricular sound in two cases with severe stenosis. An ejection sound, with the same timing as in the first group was heard or recorded in only 5 cases, all with moderate stenosis (RV P. 75 mm. or less). In one other patient the sound appeared for the first time after operation when the right ventricular systolic pressure had fallen from 110 to 55 mm. The second heart sound was abnormally widely split with a soft late pulmonary

TABLE

SUMMARY OF FINDINGS

	Simple pulmonary stenosis		
	1. Mild	2. Moderate or severe	3. Fallot's tetralogy
Electrocardiogram	Normal	Right ventricular hypertrophy	Right ventricular hypertrophy
Right ventricular systolic pressure	Under 40 mm. Hg	50–160 mm. Hg	70–115 mm. Hg
Ejection sound—			
Pulmonary	Invariably present	Uncommon	Absent
Aortic	Absent	Absent	Occasional
Second sound—			
Aortic component	Normal	Normal but may be masked by murmur at pulmonary area	Normal or accentuated
Pulmonary component	Normal	Present (85%) but intensity reduced	Absent
Degree of splitting	Increased (0·03–0·06 sec. in expiration)	Greatly increased (0·05–0·14 sec. in expiration)	—
Pulmonary systolic murmur	Soft	Loud and long, may extend past aortic component	Variable in intensity and duration

component which was heard and recorded in 28 (85%) cases (Fig. 5 and 6). Sometimes the splitting was difficult to hear, because the earlier (aortic) component was drowned in the loud systolic murmur at the pulmonary area, or because the later (pulmonary) component was very soft. The splitting was often heard more easily in the third or fourth left space where the systolic murmur was less loud. The time interval between the two components of the second sound in the expiratory phase of respiration varied from 0·05 to 0·14 sec. and was closely related to the severity of the stenosis as judged by the right ventricular systolic pressure (Fig. 10). Following a successful valvotomy, with a fall in right ventricular systolic pressure, the time interval shortened, e.g. from 0·14 to 0·07 sec. with a fall in RV systolic pressure from 150 to 55 mm., and from 0·12 to 0·06 sec. with a fall from 150 to 50 mm. The wide splitting was found to be due to delay in pulmonary valve closure caused by prolongation of right ventricular systole, there being no delay in onset of right ventricular systole (Q—RV time of 0·07 sec., identical with that found in normal subjects by Coblentz *et al.*, 1949), and no shortening of left ventricular systole (average 0·31 sec., identical with that found in 10 normal subjects). The duration of right ventricular systole ranged from 0·36 to 0·41 and averaged 0·39 sec. The pulmonary component of the second sound was always reduced in intensity on auscultation, and this was confirmed on the phonocardiogram. When both components were clearly recorded the pulmonary was always less than half the aortic in amplitude (no measurement of the absolute intensity of heart sounds and murmurs was possible). Following valvotomy the pulmonary component tended to increase in intensity.

In the five patients in whom the pulmonary component of the second sound was absent the pulmonary stenosis was more severe (average right ventricular systolic pressure 115 mm., compared with 80 mm. in the remainder). In one of them a late pulmonary component appeared for the first time after operation when the right ventricular systolic pressure fell from 150 to 55 mm.

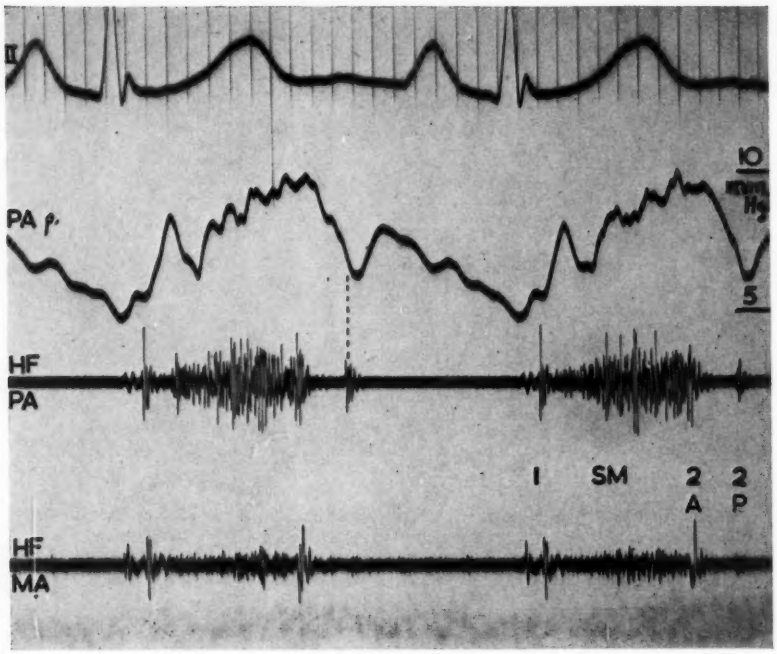


FIG. 4.—Pulmonary valve stenosis (RV P. 70/5, PA P. 10/5 mm. Hg). Later component (P2) of second sound coincides with dicrotic notch of pressure pulse from pulmonary artery (PA P.) allowing for delay of 0·02 sec.

The intensity of the pulmonary systolic murmur varied from moderately loud (grade 3) to very loud (grade 6) and was grade 4 or 5 in 28 out of 33 patients. The murmur started soon after the first sound and tended to be long. It frequently extended up to or even past the aortic component of the second sound, making this sound difficult to identify at the pulmonary area, although easily heard and recorded at the apex. The murmur always ended before the delayed pulmonary component and its maximum intensity was about mid-way between this and the first heart sound (Fig. 5 and 6).

In the four patients with pure infundibular stenosis, as judged by cardiac catheterization, the systolic murmur and second heart sound showed no consistent difference from the valvular cases (Fig. 5 and 6).

An auricular systolic murmur of low intensity was recorded in three patients, of whom two had valvular and one infundibular stenosis, but was heard only in the patient with infundibular stenosis (Fig. 7). A giant *a* wave was seen in the neck of each of these patients. An early diastolic murmur of very low intensity was also recorded in one patient with valve stenosis, but no cause was found at operation.

FALLOT'S TETRALOGY

Ventricular septal defect with a right-to-left shunt was demonstrated in every case by catheterization or angiocardiography. All had cyanosis and clinical and electrocardiographic evidence of right ventricular hypertrophy. The right ventricular systolic pressure ranged from 70 to 115 mm. Hg, and was about the same as the systemic pressure in the 18 patients who were catheterized. The

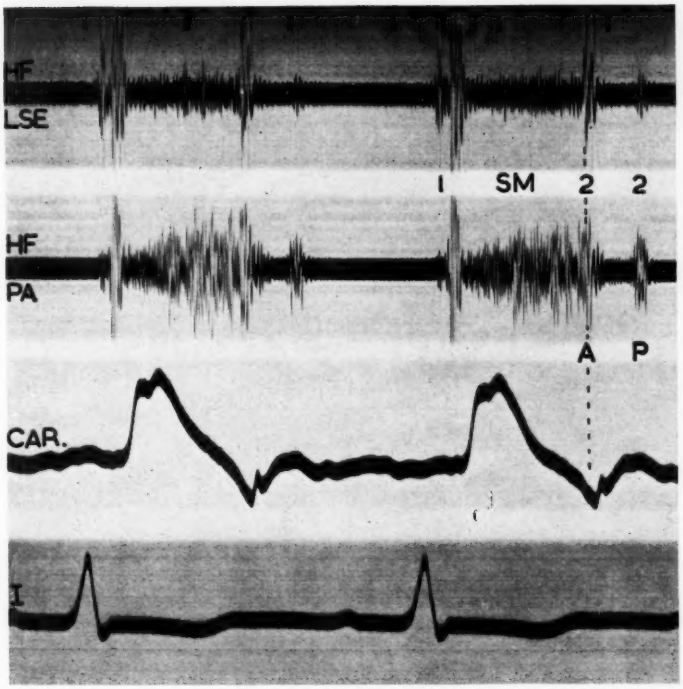


FIG. 5.—Severe pure pulmonary valve stenosis (RV P. 125/0 mm. Hg). Splitting of second sound with pulmonary component in pulmonary area 0·10 sec. after aortic component recorded from lower left sternal edge (LSE). Ejection systolic murmur extends past aortic component of second sound and stops before pulmonary component.

stenosis as seen at operation or necropsy was described as infundibular in nine cases, valvular and infundibular in five, and predominantly valvular in five. In seven cases the site of the stenosis has not yet been established.

The first sound was normal and was followed in two patients by an early systolic sound (Fig. 8). This sound was maximal at the aortic and mitral areas, uninfluenced by respiration, and 0·07 sec. after the first heart sound, i.e. later than the ejection sound in mild pulmonary stenosis (mean 0·04 sec. after the first sound). The lateness of this sound made it unlikely to be due to ejection into the pulmonary artery, which must be early in severe pulmonary stenosis with a low pulmonary artery pressure, and this was confirmed in one case where the onset of the pulmonary systolic murmur preceded the extra sound. In the same patient the extra sound followed the onset of rise of pressure in the aorta by 0·04 sec. (calculated). These findings strongly suggested that this sound was related to aortic ejection, and this belief was supported by the presence of a similar sound with identical timing in two patients with pulmonary atresia.

The second sound was always single before operation and was attributed to aortic valve closure from its relation to the dicrotic incisura of the carotid tracing (Fig. 9). No pulmonary component was recorded in any patient before operation, but in three who were studied after it the pulmonary component of the second sound became audible for the first time and was recorded. In one patient the pulmonary component first appeared 0·11 sec. after the aortic, following a Blalock operation (Fig. 11A): after valvotomy this interval decreased to 0·06 sec. (Fig. 11B).

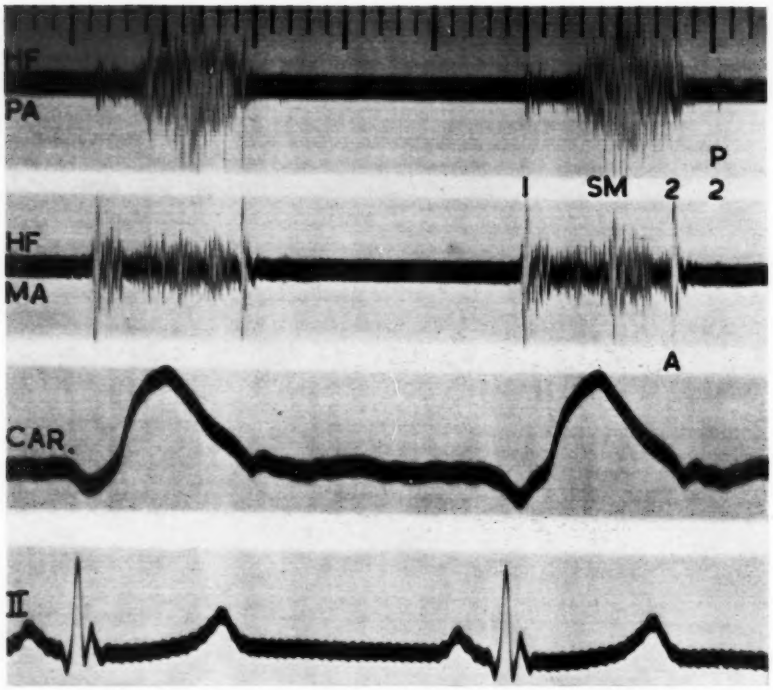


FIG. 6.—Pure infundibular stenosis (RV P. 65/5, infundibular chamber 23/5, PA P. 23/10 mm. Hg). Loud ejection systolic murmur and wide splitting of second sound (0·09 sec.) as in cases of valve stenosis.

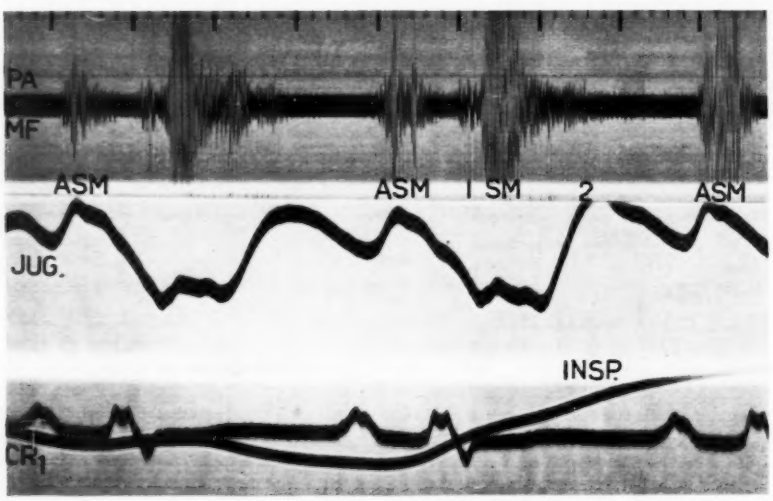


FIG. 7.—Pure infundibular stenosis (RV P. 60/4, infundibular chamber 25/4, PA P. 21/1 mm. Hg). with auricular systolic murmur (ASM), showing inspiratory increase in intensity usual in right-sided murmurs.

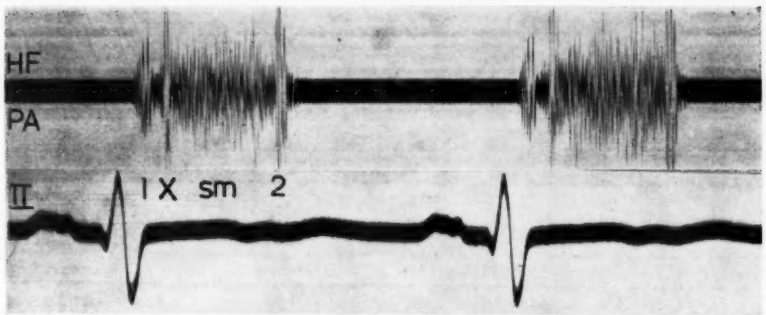


FIG.8.—Fallot's tetralogy. Aortic early systolic ejection sound (X). Single second sound.

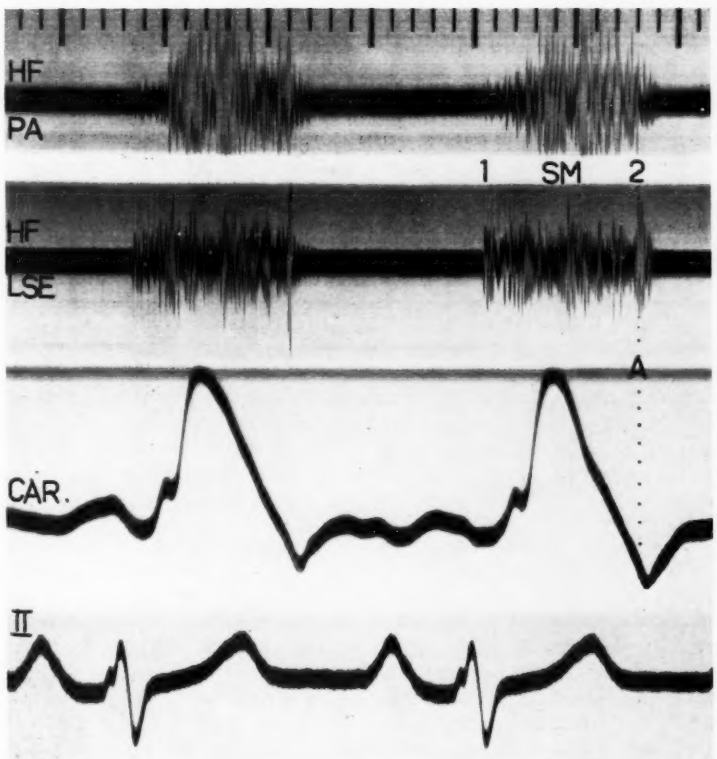


FIG. 9.—Fallot's tetralogy. Single second sound due to aortic closure; absent pulmonary component. Ejection systolic murmur extends up to aortic closure.

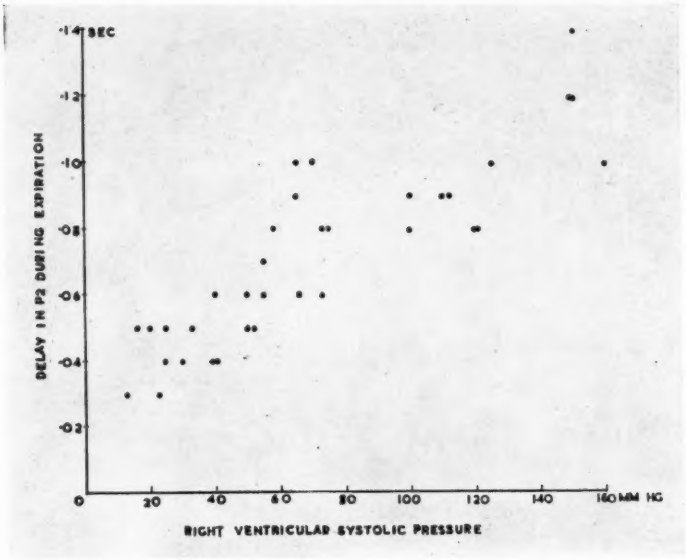


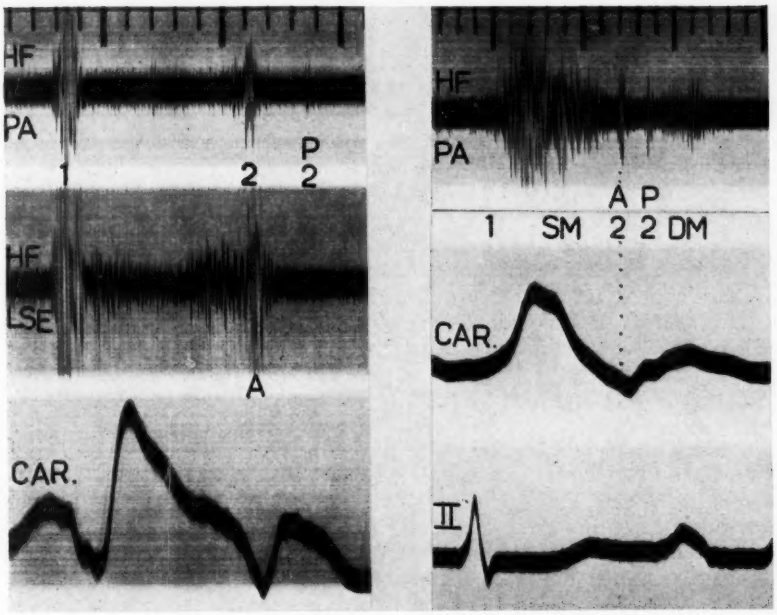
FIG. 10.—Relation of delay in pulmonary valve closure (width of splitting of second sound) to right ventricular systolic pressure in all cases in which a pulmonary component was recorded (Groups 1 and 2).

The intensity of the pulmonary systolic murmur in the patients with Fallot's tetralogy varied from grade 2 to grade 6, but was usually less loud (grade 3 or 4) than in the second group (grade 4 or 5). In seven patients the murmur was short, finishing before aortic closure, with a crescendo in mid-systole (Fig. 12, top channel), but in the majority the murmur (Fig. 9) was as long as in many patients in the second group (Fig. 5 and 6). An auricular systolic murmur of low intensity was recorded in two cases, both with dominant *a* waves in the neck. Early diastolic murmurs developed after operation in three cases (Fig. 11B), and were attributed to pulmonary incompetence, but insufficient studies were made for the incidence of this complication to be determined. The findings in the three groups are summarized in the table.

DISCUSSION

The anatomical and hæmodynamic features of pulmonary stenosis produce characteristic changes in the heart sounds. Dilatation of the pulmonary artery is associated with a pulmonary early systolic ejection sound in mild cases. The obstruction to right ventricular discharge prolongs right ventricular systole resulting in late closure of the pulmonary valve (Leatham, 1951, 1952; Borges *et al.*, 1952; Kjellberg *et al.*, 1955; Vogelpoel and Schrire, 1955) and produces an ejection type of systolic murmur (Leatham, 1955).

The pulmonary early systolic sound was present in all patients with mild stenosis including five of the mildest cases in the second group. It was always associated with a pressure change at valve level and obvious enlargement of the pulmonary artery. This sound was probably responsible for the impression of accentuation of the first sound mentioned by other authors, and Lian and Welti (1937) had described a protosystolic sound in cases of " congenital dilatation of the pulmonary artery ". A pulmonary early systolic sound also occurs with dilatation of the pulmonary artery



A B

FIG. 11.—Fallot's tetralogy after operation. (A) After a Blalock operation pulmonary component of second sound appeared, 0·11 sec. after aortic component. (B) After subsequent valvotomy interval decreased to 0·06 sec. and there was an early diastolic murmur (DM).

from pulmonary hypertension and has been shown to fall in the ejection phase (Leatham and Vogelpoel, 1954). The early systolic sound in pulmonary stenosis has the same quality, site of maximum intensity, and relation to respiration; it also is, therefore, considered to be a pulmonary ejection sound. The sound was earlier in pulmonary stenosis (av. 0·05 sec. after first sound) than in pulmonary hypertension (av. 0·07 sec.) because the isometric time was shorter with the low diastolic pressure in the pulmonary artery. It was a sign of slight or moderate valve stenosis and was never found in severe cases or with infundibular stenosis in this series. The ejection sound is presumably caused by sudden distension of the dilated pulmonary artery and its absence in severe pulmonary stenosis may be related to slow rise of pulmonary artery pressure, and in infundibular stenosis to lack of dilatation of the pulmonary artery.

The dilated aorta found in Fallot's tetralogy and in pulmonary atresia was sometimes associated with an aortic ejection sound. This sound can usually be differentiated from the pulmonary sound by its site, lateness, and lack of variation with respiration. In practice, however, the need to differentiate between them does not arise since the pulmonary ejection sound occurs only in mild cases without cyanosis, and the aortic only in severe cyanotic cases when it indicates over-riding of the aorta rather than an inter-atrial shunt as the cause of the cyanosis. The aortic sound is seldom *audible* in Fallot's tetralogy, because it tends to be drowned by the loud systolic murmur. Conversely the sound is clearly heard in pulmonary atresia because a pulmonary systolic murmur is absent.

The second heart sound in the pulmonary area consists of aortic and pulmonary components. In healthy subjects the two components are about equal in intensity and are fused or closely split in expiration, separating during inspiration from delay in the pulmonary component. The interval

between the two components does not normally exceed 0·03 second in the expiratory phase of continuous respiration (Leatham, 1954).

The aortic component of the second sound can be heard in all patients with pulmonary stenosis, as clearly stated by Abrahams and Wood (1951), and may even be accentuated in Fallot's tetralogy. The pulmonary component was heard and recorded in all our cases with mild pulmonary stenosis and was of normal intensity. In 85 per cent of the more severe cases with pure pulmonary stenosis the pulmonary component was also present, though of reduced intensity. In assessing the severity of the stenosis, however, diminution of the intensity of the pulmonary component was less significant than its separation from the aortic component, which was always greater than normal in the expiratory phase of respiration. Of the possible causes for the increased separation of the two components, shortening of left ventricular systole and late activation of the right ventricle were excluded. It was found to be due to delay of pulmonary valve closure from prolongation of right ventricular systole and was a feature of all cases of pulmonary stenosis.

The time interval between aortic and pulmonary closure is a particularly accurate measure of the severity of the stenosis since the prolongation of right ventricular systole is measured in relation to left ventricular systole in the same patient and in the same cardiac cycle. This time interval is a useful guide to the right ventricular systolic pressure to which it generally bears a surprisingly close relation, considering that phonocardiography and catheterization were usually carried out at different times.

In contrast to this finding, the degree of right ventricular hypertrophy on the electrocardiogram was less closely related to the right ventricular systolic pressure. In eight patients with right ventricular systolic pressures of 120 mm. or more, the degree of right ventricular preponderance varied from slight to great, and in nine patients with moderate preponderance the right ventricular systolic pressures ranged from 50 to 160 mm. Where pulmonary valve closure can be recorded the phonocardiogram is a more reliable method of assessing severity than the electrocardiogram, especially in children in whom the normal right ventricular dominance makes the cardiographic assessment of right ventricular hypertrophy difficult.

While the soft late pulmonary component of the second sound could usually be discerned by careful auscultation, the aortic component, though clear at the apex, was frequently obscured at the pulmonary area by the loud long systolic murmur. Between the apex and pulmonary area both components could sometimes be heard, but phonocardiograms taken synchronously from the two areas were often needed to appreciate this sign and to obtain the exact time interval between the two components.

The frequency with which the pulmonary component can be heard in pure pulmonary stenosis contrasts with its rarity in Fallot's tetralogy, where it was absent in all our cases before operation because of the greater diminution of pulmonary artery flow in Fallot's tetralogy (Leatham, 1954). This was also found by Vogelpoel and Schrire (1955) whose clear recordings showed a pulmonary component in only 3 (heard in one) of their 18 cases of Fallot's tetralogy. In our cases, the average pulmonary artery flow was 2·7 litres a minute in the Fallot group compared with 5·4 litres in pure pulmonary stenosis, confirming the findings of Soulié *et al.* (1951*a*). The greater diminution of pulmonary flow in Fallot's tetralogy is probably due more to the easier outlet offered by the overriding aorta and ventricular septal defect than to any greater degree of stenosis.

An alternative explanation for the inaudibility of the pulmonary component in Fallot's tetralogy, is that the aortic and pulmonary valves close simultaneously. This is impossible since the ventricular pressure in Fallot's tetralogy at the time of aortic valve closure must be only just below the systemic diastolic pressure, and still greatly above the low pulmonary artery pressure, making it impossible for the pulmonary valve to close at this point. Hence right ventricular systole must be prolonged as in pure pulmonary stenosis. This was confirmed by the first appearance of a delayed pulmonary component (0·11 sec. after aortic closure) in one of our cases after a Blalock's operation, and in two others after valvotomy (delay 0·05 and 0·12 sec.). It follows that the presence of the pulmonary component of the second sound (recorded or heard) in rare cases of Fallot's tetralogy

should indicate a greater pulmonary flow than usual and this has been shown in one case by Vogelpoel and Schrire (1955). Similarly the absence of the pulmonary component in a few cases of severe pure pulmonary stenosis was always associated with an unusually small pulmonary flow.

With these reservations we found that the presence or absence of a pulmonary component of the second sound was of great help in differentiating between Fallot's tetralogy and pure pulmonary stenosis with cyanosis due to a reversed inter-atrial shunt.

In every patient with pulmonary stenosis there is a systolic murmur due to the ejection of blood through the narrowed infundibulum or pulmonary valve. This murmur rises to a crescendo about the mid point of right ventricular systole. Because right ventricular systole is prolonged, the murmur may go up to or past aortic closure but always finishes before pulmonary closure. In pure pulmonary stenosis the entire output of the right ventricle must be discharged through the obstructed outlet, while in Fallot's tetralogy the over-riding aorta offers an alternative pathway. Hence the pulmonary flow tends to be greater, and the systolic murmur louder, in pure pulmonary stenosis than in Fallot's tetralogy with the same degree of obstruction. This difference in intensity of the murmur is well known (Soulié *et al.*, 1951*b*). When there is considerable over-riding the pulmonary flow may be so reduced that only the maximum flow in mid-systole is sufficient to produce audible vibrations, but increased amplification shows that the murmur is longer, going at least as far as aortic closure (Fig. 12). This probably accounts for the fact that in severe cases with a short murmur the diagnosis always proved to be Fallot's tetralogy, as stated by Vogelpoel and Schrire (1955). Conversely a murmur sufficiently long to extend past aortic closure was always associated with a closed ventricular septum. In many of our patients, however, whether the diagnosis was Fallot's tetralogy or pure pulmonary stenosis, the murmur was of intermediate length extending up to but not beyond aortic closure, and was of no help in differentiating the two conditions.

The site of the obstruction, valvular or infundibular, did not appear to influence the sounds and murmurs. In four patients with normal aortic root there was good evidence from cardiac catheterization and angiocardiography that the stenosis was low infundibular rather than valvular, although operation or necropsy proof was lacking. The systolic murmur and second heart sound showed the same characteristic features as in valvular stenosis. Mannheimer and Jonsson (1954) found an earlier crescendo in two of their cases diagnosed by selective angiocardiography. We confirmed this in one case (Fig. 7), but not in others (Fig. 6). The rarity of pure infundibular stenosis and lack of proof of the diagnosis in our cases prevents definite conclusions.

Diastolic murmurs were seldom obvious. In five patients in the second and third groups auricular systolic murmurs were recorded, usually of low intensity and inaudible. In one patient with low infundibular stenosis this murmur was loud in the pulmonary area, increased on inspiration, and *a* waves were found on the pressure tracing from the pulmonary artery. All these patients had giant *a* waves in the neck and the atrial systolic pressure exceeded the pulmonary diastolic pressure. It seems reasonable to conclude that the atrial systolic murmur is caused by flow through the pulmonary valve as a result of atrial contraction.

Differential Diagnosis

Other possible causes for a pulmonary systolic murmur are increased pulmonary flow and dilatation of the pulmonary artery. The characteristics of the second sound are of considerable help in differentiating these conditions. In atrial septal defect the increased pulmonary flow causes a short ejection systolic murmur, of similar pattern to that found with mild pulmonary stenosis, and wide splitting of the second heart sound which has come to be recognized as an obvious physical sign (Barber *et al.*, 1950). The pulmonary component is then of normal or increased intensity (often transmitted to the apex) and the separation of the two components does not alter with respiration and does not exceed 0·05 sec. (Leatham and Gray, 1956), unlike pulmonary stenosis.

In dilatation of the pulmonary artery without increased flow, as in pulmonary hypertension,

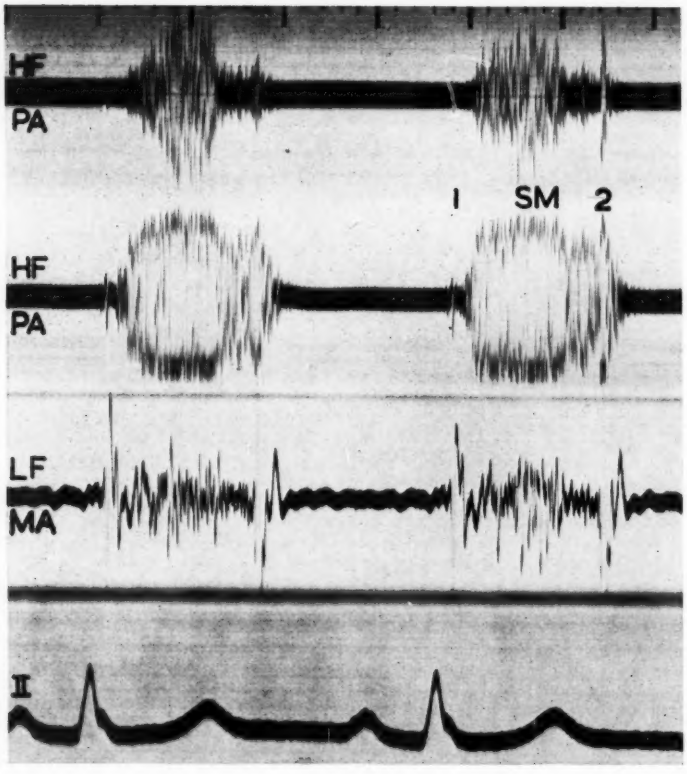


FIG. 12.—Fallot's tetralogy. Ejection systolic murmur with crescendo in early or mid-systole dwindling before single second sound (top channel). Increased amplification (with voltage limitation) shows that murmur continues past aortic closure (second channel).

there may be a soft or moderately loud ejection systolic murmur, but there is normal close splitting of the second sound with accentuation of the pulmonary component and frequently a pulmonary diastolic murmur.

Where there is increased flow, without dilatation of the pulmonary artery, in anæmia, thyrotoxicosis, pregnancy, and other high output states, the systolic murmur is seldom loud, and splitting of the second sound is normal and confined to the inspiratory phase of respiration since the high flow is affecting both sides of the heart equally. The pulmonary component is of normal intensity. The innocent pulmonary ejection murmur so commonly found in healthy young people is also associated with normal splitting of the second sound.

The harsh pansystolic murmur of ventricular septal defect may closely resemble the murmur of pulmonary stenosis, but its site of maximum intensity is lower, and splitting of the second sound is normal or only slightly increased in width with no diminution of the pulmonary component. Attention to the second heart sound is thus of great importance in deciding the cause of a pulmonary systolic murmur. Only in pulmonary stenosis is the pulmonary component of reduced intensity (or even absent) and separated from the aortic component by more than 0·05 sec.

Summary

A graphic analysis of the heart sounds and murmurs has been made in 70 patients with pulmonary stenosis. The diagnosis has been confirmed by cardiac catheterization or operation in all. The patients fell into three groups each with typical auscultatory and phonocardiographic findings.

In the first group the stenosis was mild and isolated, the electrocardiogram normal, and the right ventricular systolic pressure less than 40 mm. Hg. The first heart sound was invariably followed by an early systolic ejection sound giving the impression of wide splitting of the first sound at the pulmonary area. Splitting of the second heart sound was abnormally wide. The pulmonary component was delayed and was of normal intensity. There was a soft mid-systolic ejection murmur.

In the second group the stenosis was moderate or severe (right ventricular pressure 50–150 mm.) with a normal aortic root. In some there was cyanosis from an inter-atrial shunt. A pulmonary ejection sound was found only in the milder cases. The pulmonary component of the second sound was present in 85 per cent and was soft and greatly delayed. The interval between aortic and pulmonary components was closely related to the right ventricular systolic pressure. The pulmonary component was absent only in the most severe cases. The loud ejection systolic murmur extended up to, and sometimes beyond, the aortic component of the second sound.

The third group consisted of patients with Fallot's tetralogy. The greater reduction of pulmonary flow was associated with a shorter and softer systolic murmur in some cases, and with absence of the pulmonary component of the second sound except following operation.

We would like to express our gratitude to the Physicians to the Heart Hospital for encouraging us to study their cases and to Dr. William Evans and Dr. Paul Wood for much helpful advice. We are also indebted to the technical staff of the Institute of Cardiology for help with the recordings.

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ATRIAL SEPTAL DEFECT IN CHILDREN

BY

JOAN WAGNER * AND GERALD R. GRAHAM

From The Congenital Heart Unit, The Hospital for Sick Children, London

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This paper has a two-fold purpose: first, to present the signs and symptoms of atrial septal defect and thus outline the findings that help in making the clinical diagnosis, and secondly, to show that correct and early diagnosis is important, because this anomaly gives rise to serious, although frequently obscured, symptoms and disabilities more often than has been generally realized.

Clinically, atrial septal defect may be defined as a developmental anomaly of the atrial septum that permits a shunt of blood between the two atria. Over 300 cases of atrial septal defect have been recorded in the period 1765–1954. The first mention of a case was probably in a report by Morgagni (1765). This was followed by several reports during the nineteenth century (Corvisart, 1811; Louis, 1826; Ecker, 1839; Mayne, 1848; Peacock, 1860; Martineau, 1865; Rokitansky, 1875). When, in 1934, Roesler collected all the cases (as he thought) previously described, adding one of his own, a total of 62 had been reached. Since then the reporting of such cases has avalanched. Thus, in 1940, Tinney reviewed 24 cases from 1934–1938, Bedford *et al.* 53 in 1941, Cosby and Griffith 35 in 1949, and at least 200 other examples have been put on record.

The clinical diagnosis of this condition had not been well established until recently, and even now many features are disputed. With the introduction of special techniques of investigation, notably cardiac catheterization and angiocardiography, the diagnosis in life is more firmly established than before. At the same time, correlation of these investigations with the clinical findings has provided an objective check on the clinical diagnostic criteria. With the advance in cardiac surgery, which has led to several techniques for atrial septal closure, precision in diagnosis has become essential. Satisfactory clinical criteria are necessary to select cases for additional studies, such as cardiac catheterization. With these problems in mind we have reviewed the clinical profiles of 133 children with atrial septal defect.

Material and Methods

Out of the current list of about 1500 patients who are regularly followed in the congenital heart clinic of this hospital, 133 were found to have an atrial septal defect without other congenital cardiac anomalies. The majority of these patients had originally been referred to this clinic because of murmurs heard on routine examination. In about one-fourth of the cases the diagnosis has been confirmed by cardiac catheterization.

All patients had clinical investigations consisting of history and physical examination. Most patients had an electrocardiogram consisting of standard and unipolar limb leads V1 to V5, and in may cases V3R and V5R. Frequently, serial electrocardiograms had been taken over several years. All patients were studied fluoroscopically, including a barium swallow, and X-ray films were taken in at least two positions (postero-anterior and lateral). In addition 17 phonocardiograms and 17 jugular pulse tracings were recorded.

* Present address: Department of Medicine, University of Witwatersrand, Johannesburg, S.A.

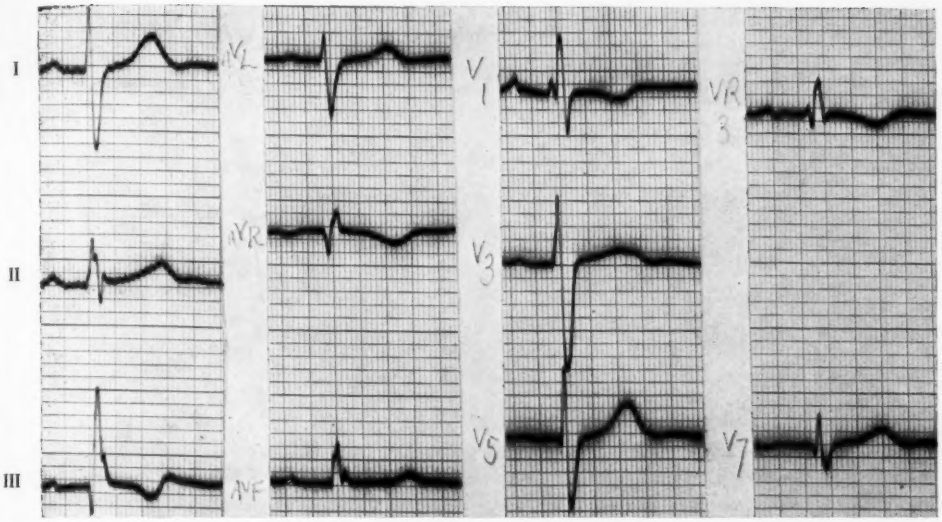

FIG. 1.—Electrocardiogram of patient, aged 10 years. Incomplete right bundle-branch block. Additional pattern of right ventricular hypertrophy equivocal. Cardiac catheterization proved atrial septal defect, with mild pulmonary arterial hypertension. (Standardization: 1 cm. = 1 mv.; time interval: 0·1 sec. between heavy vertical lines.) V3R and V7 are shown on the right.

All cases in which the features were not sufficiently well defined to make the diagnosis with certainty have been omitted. Our follow-up system has often allowed us to arrive at the correct diagnosis in cases where early in the course of the disease the diagnosis was in doubt. The group can be considered a representative sample of children with this anomaly. The incidence of this defect among our patients with congenital heart disease is similar to percentages in large autopsy series (Abbott, 1936; McGinn and White, 1933; Gibson and Clifton, 1938; Ingham, 1938).

RESULTS

History. None of the mothers had had rubella or other significant illnesses during pregnancy. Labour and delivery presented no abnormal features and there was no correlation with sibling order. The neonatal period was normal in all except one infant who died aged two months. No gross abnormalities of intellectual development were observed, but neither qualitative nor quantitative tests were performed.

For the purpose of presenting the symptoms, the cases are divided into two groups according to heart size, to test whether there was a significant difference in symptoms related to this datum. The symptoms are further subdivided into those, if any, with which the child presented and those appearing subsequently.

The two outstanding symptoms were breathlessness (in 65 patients) and frequent chest infections (in 70). It should be noted that in three-quarters of the patients with normal or only slightly enlarged hearts and in half of those with much enlargement, symptoms had been insufficient for the parents to seek medical advice, the murmur having been heard on routine medical examination. However, subsequent questioning revealed that actually only one-fifth of the patients had been entirely free of symptoms, and that almost all of these had hearts of normal size.

Cyanosis at some stage, usually only temporary, was said to have been seen by the parents of one-third of the patients.

When the symptoms of breathlessness, lassitude, and cyanosis (parental observation) were related to the patient's age when they were first observed, no great difference was found between the cases with normal or slightly enlarged hearts and those with large hearts. Similarly, when the whole group was divided into three according to age at onset of symptoms (under 1 year; 1–5 years; 5–10 years), no difference was found between patients with normal (or slightly enlarged) and those with large hearts.

Rather surprisingly, a lack of correlation between age at the time of onset of first symptoms on one hand and heart size on the other was also shown by a similar number of cases falling into each of the three age groupings.

Signs. A tumultuous apex beat and evidence of right ventricular enlargement by percussion and palpation were often present, but criteria are not standardized enough to allow tabulation.

The following were the physical signs found to be most frequent and most reliable in making the diagnosis.

(1) Enlargement of the heart involving mainly the right side (found clinically in over one-third of the series);

(2) a loud and (often widely) split pulmonary second sound (all cases);

(3) a systolic murmur at the pulmonary area (grade II in 75 per cent; grade III or IV in 22 per cent of cases), sometimes accompanied by a palpable thrill in this area (26%); and

(4) an apical diastolic murmur (30%).

Sex incidence was equal. The small size of the children was an outstanding feature of the group, especially as regards weight (62 per cent were of normal height, but only 25 per cent of normal weight).

In many cases the jugular pulse (Reinhold, 1955) showed very tall *v* waves, presumably the result of increased right atrial inflow, but normal *a* and *c* waves. Prominent *a* waves, on the other hand, were found only when pulmonary hypertension co-existed, but were not diagnostic of atrial septal defect *per se*. The incidence of these findings is not recorded, because they were not looked for in all cases.

Associated Diseases and Anomalies. Other cardiac anomalies are excluded from this series. Rheumatic fever, with or without heart disease, occurred in only one case. Subacute bacterial endocarditis was never diagnosed. Physical abnormalities, other than of growth, were uncommon. Two cases showed mongolism. In twenty cases there were physical abnormalities such as pigeon chest and Harrison's sulcus, but the anomalies were severe, in two patients only, in one idiot and in one with an Ellis van Creeveld syndrome.

Electrocardiogram. Of the 13 patients with standard leads almost half showed abnormalities. On the basis of the remainder in whom additional unipolar limb and præcordial leads were also taken, it is likely that abnormalities were missed in these. In an analysis of the findings, it has been thought fairest to consider this group of 120 patients separately (Group B). Ninety per cent of the multi-lead electrocardiograms were abnormal, over 85 per cent of them showing right ventricular hypertrophy, right bundle-branch block (complete or incomplete), or both. Slightly more than half had right ventricular hypertrophy, frequently associated with some form of right bundle-branch block, while two-thirds of this group showed complete or incomplete right bundle-branch block. P wave abnormalities were infrequent and did not correlate well either with right atrial size or pressure where this was obtained during cardiac catheterization.

Fluoroscopic and X-ray Examination. The typical radiological changes were right-sided cardiac enlargement, prominent right ventricular outflow tract, a pulmonary artery with active pulsation, and increased pulmonary vascularity with dilated main pulmonary artery branches (Fig. 2). Right atrial enlargement was not specifically diagnosed by us, because its radiological criteria are so ill-defined and controversial. Barium swallow showed typically a small aortic, a long pulmonary, and a normal cardiac impression. The films were at times useful as a permanent record and in judging pulmonary vascular changes. Fluoroscopy was by far the most informative examination.

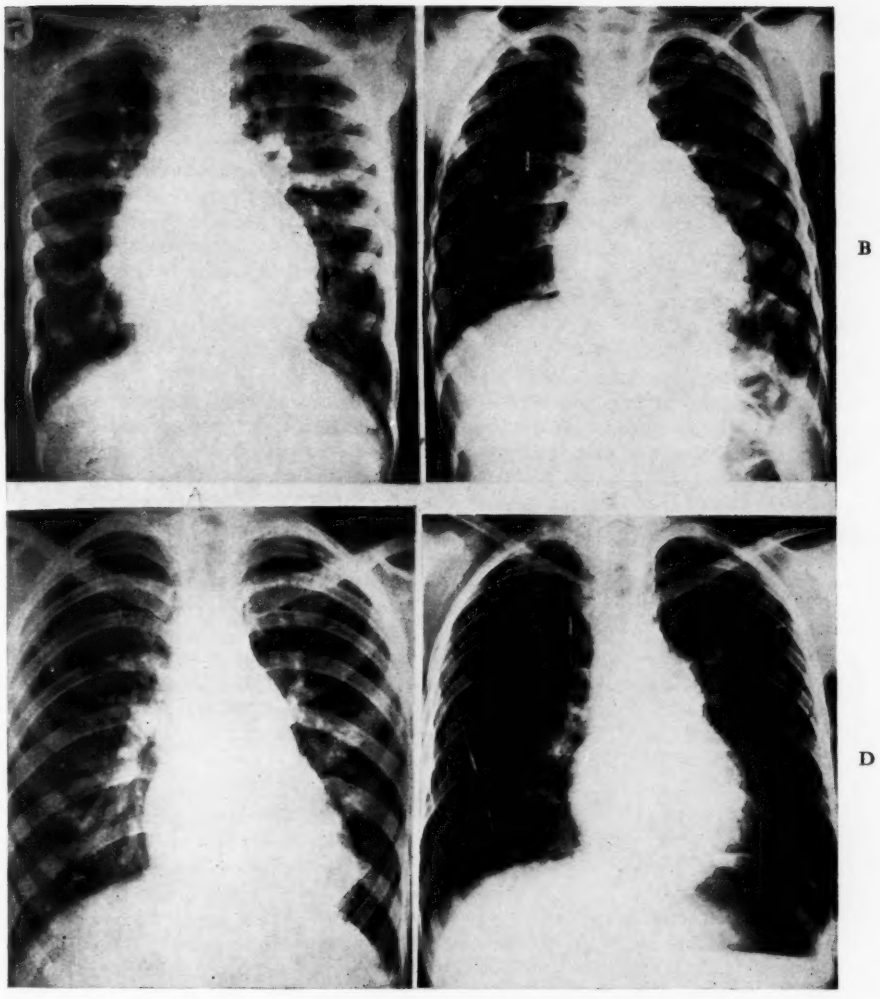

FIG. 2.—X-rays of chest in atrial septal defect. (A) and (B). Patiends with normal pulmonary artery pressures. (C) and (D). Patients with severe pulmonary artery hypertension. (For explanation see text.)

Deaths. Six patients died, aged two months, four months, twenty months, three, four, and five years, respectively. Congestive heart failure was the cause of death in four, bronchopneumonia in one, and the sixth died after an attempt at surgical closure. The average age of death in the Roesler (1934) series was 36, in Welch and Kinney's series 33 (1940) and in Burnett and White's 39 years (1945).

Discussion

The Symptoms. Breathlessness and frequent chest infections were the two outstanding symptoms. It would be tempting to relate both to the increased pulmonary flow, but other congenital cardiac defects with left-to-right shunts, such as patent ductus, ventricular septal defect or Eisenmenger's complex, do not lead to these complaints to the same extent. Data are, however, too sparse to correlate the amount of total pulmonary flow with symptoms in such anomalies.

Our data show that very few of the children remained without symptoms while under observation, although many of them had the defect diagnosed on routine medical examination. Inadequate gain in weight was the most striking clinical finding. While comparative data are meagre, it is our experience that no other acyanotic congenital heart disease shows this feature either as frequently or as severely. On the whole, these findings are comparable with those of other authors. The frequency of symptoms is generally stressed (Barber *et al.*, 1950; Bedford *et al.*, 1941; Burnett and White, 1945; Cosby and Griffith, 1949; Roesler, 1934).

The Signs. The physical signs that we found agree with those of the more recent reports. For many years following the first clinical description of atrial septal defect, the typical murmur was thought to be " presystolic and synchronous with atrial systole," a view held by Tilbury Fox in 1859 and still supported by Carpenter in 1909. It is by now agreed, however, that the typical and usual murmur is systolic. Atrial septal defects without murmurs have been described (Peacock, 1860; Lumsden, 1946) but in the absence of a murmur one would hesitate to make the diagnosis and rather classify the condition as anomalous drainage of the pulmonary veins which may give signs and symptoms of atrial septal defect in the absence of a murmur.

The cause and origin of the systolic murmur are unanswered problems. It may be due to the interatrial flow of blood, which is maximal during ventricular systole. Usually the murmur is high along the left sternal border and of rather limited transmission, but cardiac size and position and extracardiac factors may influence the loudness and location of any murmur to make these details variable. Because interatrial pressure gradients are small, flow through the defect, although it may be large, does not cause the type of turbulence and vibration that, in interventricular septal defects, give rise to a loud and coarse murmur. A thrill is, therefore, felt only very rarely from this cause alone.

In almost one-third of our cases an apical diastolic murmur was heard. Other authors have reported a similar incidence. The production of this murmur and its possible relation to Lutembacher's syndrome have caused considerable controversy. Both autopsy findings and observation at the time of surgical closure have shown that in many cases, particularly if the shunt is large, the left ventricle, including the mitral valvular ring, failed to develop to their normal proportions. An apical diastolic murmur may, thus, be due to turbulence created at a hypoplastic, but otherwise normal, mitral valve from which, due to its small size, a considerable portion of left atrial inflow is shunted across the defect as this route offers less resistance to the flow. Another suggested cause is the large increase in flow through the tricuspid valve, the murmur being due to " relative " tricuspid stenosis. Pulmonary valvular regurgitation with an unusual transmission of its murmur has been given as another explanation. Finally, a late diastolic or presystolic murmur may be due to the brief but rapid shunt during atrial contraction when the pressure in the left atrium may exceed that in the right more than during other parts of the cardiac cycle.

The nature of the diastolic murmur is a matter for speculation. Other conditions may cause this murmur (e.g. patent ductus arteriosus, ventricular septal defect). It is important to know whether mitral stenosis co-exists. This syndrome has become associated with the name of Lutembacher (1916 and 1936). The frequency of this combination has never been satisfactorily settled. In several large unselected autopsy series the incidence ranged from 0·01 per cent to 0·03 per cent (Gelfman and Levine, 1942; McGinn and White, 1933; Nadas and Alimurung, 1952). Of 100 cases of acyanotic congenital heart disease, which were later examined post mortem, an apical diastolic murmur had been heard in 19, of whom 6 had an atrial septal defect; mitral stenosis was

absent in all (Nadas and Alimurung, 1952). Cosby and Griffith (1949) likewise found no case of mitral stenosis in 19 cases of atrial septal defect.

Our own observations support the view that Lutembacher's syndrome is exceedingly rare, and that apical diastolic murmurs frequently occur in uncomplicated atrial septal defect.

In addition to the murmurs, the character of the second sound heard in the pulmonary area is the most important physical sign. It was significantly loud and split in all our cases. In atrial septal defect the split is usually conspicuously wide or even palpable and can be attributed either to delay in emptying of the overfilled right ventricle, to bundle-branch block, or both. The pulmonary element is loud, either due to the proximity of the dilated pulmonary artery to the chest wall, pulmonary hypertension or the increased systolic filling of the main pulmonary vessels. However, the " split " may become less marked and even disappear with the development of pulmonary hypertension.

Cyanosis was occasionally observed in our patients. But in only ten had it become permanent. Since the occurrence of cyanosis in atrial septal defect uncomplicated by other congenital anomalies depends on the rise of right atrial pressure until it exceeds that of the left, the presence of a right-to-left shunt presupposes the existence of pulmonary and right ventricular hypertension resulting from increased pulmonary vascular resistance. The cause or causes of the increased resistance are still under dispute, and consequently there is no consensus whether such changes are wholly or partially reversible. But it is possible that the reversal of the interatrial shunt is a danger signal that circulatory changes may have progressed beyond the point where much benefit can be expected from surgical closure.

Subacute bacterial endocarditis, not found in any of our own cases, is an extremely rare complication judging by previously recorded series. Only six such cases have been found (Abbott, 1938; Bedford *et al.* 1941; Griffith, 1906), two of whom had the vegetations on the septal defect (Tinney and Barnes, 1947; Jacobius and Moore, 1938).

Only one of our patients contracted rheumatic fever. Of 64 cases described by Roesler, 41 had rheumatic fever, of whom 61 per cent had mitral valvular lesions. But actually only 6 were of the button-hole type, the rest varying from thickening of the valves to mitral insufficiency. These figures, taken together with those of Lutembacher's syndrome quoted previously, make one rather sceptical of Burnett and White's dictum (1945) that mitral valvular disease should be suspected rather than rejected in every case of atrial septal defect.

Associated physical abnormalities, other than smallness of weight and shape of chest, are rare in our series, and have not been commonly reported by others.

The Electrocardiogram. Some type of right bundle-branch block was found in 60 per cent of the electrocardiograms. Right ventricular hypertrophy was present in 67 cases, associated with complete or incomplete right bundle-branch block in 38. In a few instances this combination could be seen to have developed from incomplete right bundle-branch block in two to three years. It must be remembered that an identical pattern can be found in pulmonary stenosis and in other conditions (Barber *et al.*, 1950). The cause of the block is not certain, but it is probably associated with dilatation and hypertrophy of the right ventricle rather than with a local lesion in the interventricular septum.

Correlating the electrocardiogram with pulmonary artery pressures, where these were known, there was always right ventricular hypertrophy in the presence of pulmonary hypertension, but right ventricular hypertrophy also occurred where pressure was normal. It therefore seems that increased " flow " hypertrophy is indistinguishable from " pressure " hypertrophy electrocardiographically. The only normal electrocardiogram among those patients studied by cardiac catheterization was in a case with normal right ventricular pressure and a small interatrial shunt.

X-ray Examination. This we found a crucial part of the clinical evaluation for several reasons. First, it aids significantly in differential diagnosis. Secondly, the degree of pleonæmia of the lungfields provides a measure of the size of the left-to-right interatrial shunt. Thirdly, the results

TABLE I

SYMPTOMS OF ATRIAL SEPTAL DEFECT CLASSIFIED ACCORDING TO HEART SIZE

	82 patients with normal or slightly enlarged hearts	51 patients with large hearts
Presenting symptoms		
A. Incidentally found murmur	60	27
B. Found with symptoms related to heart disease	23	24
i. Inadequate growth	11	2
ii. Frequent chest infections	7	11
iii. Breathlessness	2	3
iv. Palpitations	1	3
v. Chest pain	1	0
vi. Attacks of cyanosis	0	1
Subsequent symptoms		
i. None	22	5
ii. Breathlessness	31	29
iii. Lassitude	16	12
iv. Frequent chest infections	30	22
v. Cyanosis	14	18
vi. Inadequate growth	12	4
vii. Palpitation	2	3
viii. Anginal pain	2	0
ix. Œdema	0	1
x. Dysphagia	0	1

TABLE II

ELECTROCARDIOGRAPHIC FINDINGS IN 133 CASES OF ATRIAL SEPTAL DEFECT

		Nos.
A. Electrocardiograms with 3 standard limb leads only (13 cases)		
Normal		7
Abnormal		6
Right ventricular hypertrophy		3
Right bundle-branch block		2
Dextrocardia		1
B. Electrocardiograms with at least 3 standard limb and 3 unipolar præcordial (V) leads (120 cases)		
Normal		12
Abnormal		108
(*a*) Non-specific		2
(*b*) Right ventricular hypertrophy		
Uncomplicated		28
With complete right bundle-branch block		11
With incomplete right bundle-branch block		25
	Total	64
(*c*) Right bundle-branch block		
Uncomplicated		14
With right ventricular hypertrophy		11
	Total	25
(*d*) Incomplete right bundle-branch block		
Uncomplicated		26
With right ventricular hypertrophy		25
	Total	51
(*e*) Abnormal P waves (associated with other electrocardiographic abnormalities)		10
(*f*) A-V block (5 associated with other electrocardiographic abnormalities)		7
Partial		5
Complete		2

of fluoroscopy and the inspection of the X-ray films give one a hint about the presence of pulmonary hypertension. The combination of right ventricular hypertrophy, prominent pulmonary conus, large pulmonary arteries, but an abrupt ending of the root branches into small, tortuous vessels with a discrepancy between the size of the central arteries and the peripheral vascularity have correlated well with the presence of pulmonary hypertension when this could be checked by cardiac catheterization. Because the presence or development of pulmonary hypertension is of importance in selecting patients for further study careful attention should be paid to this radiological appearance, although our own observations do not show how far its presence or absence is diagnostic. A striking, and unexpected, finding in this series was the slight correlation between heart size and symptoms (Tables I and II), so that the latter cannot be used as a reliable index of the disturbed

TABLE III

RESULTS OF X-RAY EXAMINATIONS IN 133 CASES OF ATRIAL SEPTAL DEFECT

	Normal size	Moderate increase	Much increase
Heart size	29	69	35
Pulmonary conus	32	79	22
Pulmonary artery shadow	19	56	58
Pulmonary vascular markings	19	38	64 (12 showed hilar dance)

Barium swallow showed the " typical " change of small aortic–long pulmonary–normal cardiac shadow in 67 cases.

circulatory dynamics. In fact, symptoms may be utterly misleading and it is often left to radiological examination to provide the first objective clue to the harmful consequences of an interatrial shunt (Plates A–D, Fig. 2).

SUMMARY

This paper reviews the history, physical examination, X-ray findings, and electrocardiograms of 133 children with atrial septal defect. All of the patients have been followed over a period of several years and many have been studied by cardiac catheterization.

From this series a composite profile of the child with atrial septal defect may be constructed. This anomaly often gives rise to serious symptoms and disabilities, which commonly appear in childhood. Growth is usually slightly retarded with a striking weight deficit. Breathlessness is common and chest infections frequently occur.

The heart is usually slightly enlarged. The pulmonary second sound is loud and split, the second component being accentuated. A systolic murmur is easily heard, loudest in the second or third left interspace. A soft apical diastolic murmur is common. The electrocardiogram often shows incomplete or complete right bundle-branch block, right ventricular hypertrophy, or both. The X-ray findings are of right ventricular enlargement, prominent pulmonary conus, large pulsatile pulmonary arteries and major branches, and increased vascularity of the lung fields. The presence of pulmonary hypertension and the size of the interatrial shunt can often be suspected from the radiological appearance.

This group shows a lack of correlation between presenting and subsequent symptoms on one hand and objective evidence of cardiac disease on the other.

We would like to thank Dr. R. E. Bonham-Carter for permission to publish facts about these patients, all of whom were under his care, and for his helpful criticism and advice in the preparation of this paper. We thank, too, Dr. J. Wells who examined the patients fluoroscopically, Dr. J. Reinhold who examined many of the electrocardiograms, and Mr. Derek Martin who prepared the photographs of the X-ray films.

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THE SMALL PULMONARY BLOOD VESSELS IN ATRIAL SEPTAL DEFECT

BY

DONALD HEATH AND WILLIAM WHITAKER

From the Regional Cardiovascular Centre, City General Hospital, and the University Department of Medicine, Sheffield

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The development of direct methods of recording pulmonary artery pressure by cardiac catheterization or bronchoscopically and the advance of cardiac surgery have stimulated an interest in pulmonary hypertension and have made it possible to study the relation of morbid anatomical and dynamic changes in the pulmonary circulation. In recent years there have been many reports of abnormal pulmonary vessels in patients with pulmonary hypertension and these suggest that there is a histological pattern characteristic of this disorder. Although pulmonary artery blood pressures may range from normal to levels of the order of the systemic blood pressure in patients with atrial septal defects there have been but few descriptions of lesions in the small pulmonary blood vessels in this anomaly (Welch and Kinney, 1948; and Evans, 1951) and an examination of the pulmonary vascular histology in a group of such cases seemed likely to provide further evidence of anatomical changes occurring with pulmonary hypertension.

In the present investigation the pulmonary blood vessels from a small group of patients with atrial septal defects, where the pulmonary artery blood pressures were known to range from normal to severe pulmonary hypertension, were examined histologically. The anatomical changes were related to the pulmonary artery blood pressures and there appeared to be well defined histological pictures characteristic of normal and of severely raised pulmonary arterial pressure.

Method. Specimens of lung were obtained at autopsy from five patients with atrial defect whose pulmonary artery pressures had been previously recorded by cardiac catheterization. Four died following attempts to close the septal defects while the other (Case 3) died from a paroxysm of tachycardia. Sections of lung from all cases were stained to show elastic by the Lawson modification of the Weigert-Sheridan method and counterstained with van Gieson's stain. Serial sections were examined from a block of lung in Case 3.

Results

The histological findings in the pulmonary blood vessels of the patients in this series are shown in Table I together with the pulmonary arterial pressures. In the patients with normal pressures (Cases 1 and 2) the media of the muscular pulmonary arteries (100 to 1000μ in diameter) was thin and consisted of smooth muscle, usually not exceeding 5 per cent of the external diameter of the vessel. It was bounded by thin, unsplit elastic membranes, and the adventitia was thin. The arterioles (less than 100μ in external diameter) had no media and usually there was only a single elastic lamina between a thin adventitia and the intima. The venules were identical in structure with the arterioles. There was no thrombosis and the degree of intimal sclerosis was less than would be expected as a normal age change (Heath and Whitaker, 1955*b*).

In the patients with severe pulmonary arterial hypertension the elastic pulmonary arteries were atheromatous. The muscular pulmonary arteries and pulmonary arterioles were grossly abnormal

TABLE I

THE PULMONARY ARTERIAL PRESSURES AND HISTOLOGICAL FEATURES OF THE MUSCULAR PULMONARY ARTERIES AND ARTERIOLES IN ATRIAL SEPTAL DEFECT

Case	Sex	Age	Pulmonary artery mean pressure (mm. Hg)	Vessels below 100μ in external diameter		Muscular pulmonary arteries		
				Distinct muscular media with two laminæ	Severe intimal proliferation of fibrous tissue exceeding normal age change	Medial hypertrophy (media exceeding 15% of external diameter of vessel)	Severe intimal proliferation of fibrous tissue exceeding normal age change	Thick adventitia
1	F	34	16	−	−	−	−	−
2	F	53	20	−	−	−	−	−
3	F	29	58	+	+	+	+	+
4	F	39	70	+	+	+	+	+
5	F	25	108	+	+	+	+	+

(Fig. 1 and 2). The media of the small muscular pulmonary arteries was hypertrophied to a thickness exceeding 15 per cent of the external diameter of the vessel (Fig. 1C and D). The elastic membranes were thick. The adventitia was thick and fibrous and in some there was intimal proliferation of fibroelastic tissue leading to partial occlusion of the vessel (Fig. 1C). The pulmonary arterioles (less than 100μ in diameter) (Fig. 1A and B) had a distinct muscular media lined by thickened internal and external elastic membranes. There was intimal proliferation of fibroelastic tissue (Fig. 1A and B). The adventitia was thick and fibrous. In some the proliferated intimal fibrous tissue had completely disorganized the structure of the vessel. There was intimal fibrosis in the pulmonary veins.

In Cases 3 and 4 many of the small muscular pulmonary arteries and the hypertensive arterioles terminated by sudden dilatation to form thin-walled vessels which were lined by a single elastic lamina and filled by what appeared to be organizing blood clot which had undergone multiple recanalization by thin-walled capillaries. Fig. 2A shows a hypertensive pulmonary arteriole of external diameter 100μ which has expanded to form a dilated thin-walled vessel, 195μ in diameter. The expanded termination of the hypertensive arterioles narrowed abruptly to form capillaries which had patent lumina about 10μ in diameter (Fig. 2A and B). Some of the arterioles ended normally in patent capillaries without first undergoing dilatation.

DISCUSSION

It would appear from this study that there are characteristic histological appearances in the pulmonary vasculature in atrial septal defect with normal pulmonary artery blood pressure and severe pulmonary arterial hypertension. Heath and Whitaker (1955*a*) reported identical findings in patients with patent ductus arteriosus and it seems, as might be expected, that these appearances are unrelated to the underlying cardiac anomaly associated with the pulmonary hypertension.

In Cases 1 and 2 of the present series of patients with atrial septal defect and in eight patients with patent ductus arteriosus reported by Heath and Whitaker (1955*a*) the pulmonary blood vessels were normal when there was a high pulmonary blood flow and a normal pulmonary artery blood pressure, which suggests that anatomical changes in the blood vessels of the lung do not follow directly from an increased pulmonary blood flow. Similarly Welch and Kinney (1948) studied 25 cases of atrial septal defect and found that in the 13 uncomplicated by an additional cardiac anomaly the pulmonary vascular lesions were not greater than those in a control group of comparable ages. Only one of these cases had been subjected to cardiac catheterization and the pulmonary artery pressure was found to be 35/10 mm. Hg with a pulmonary blood flow of 14 litres

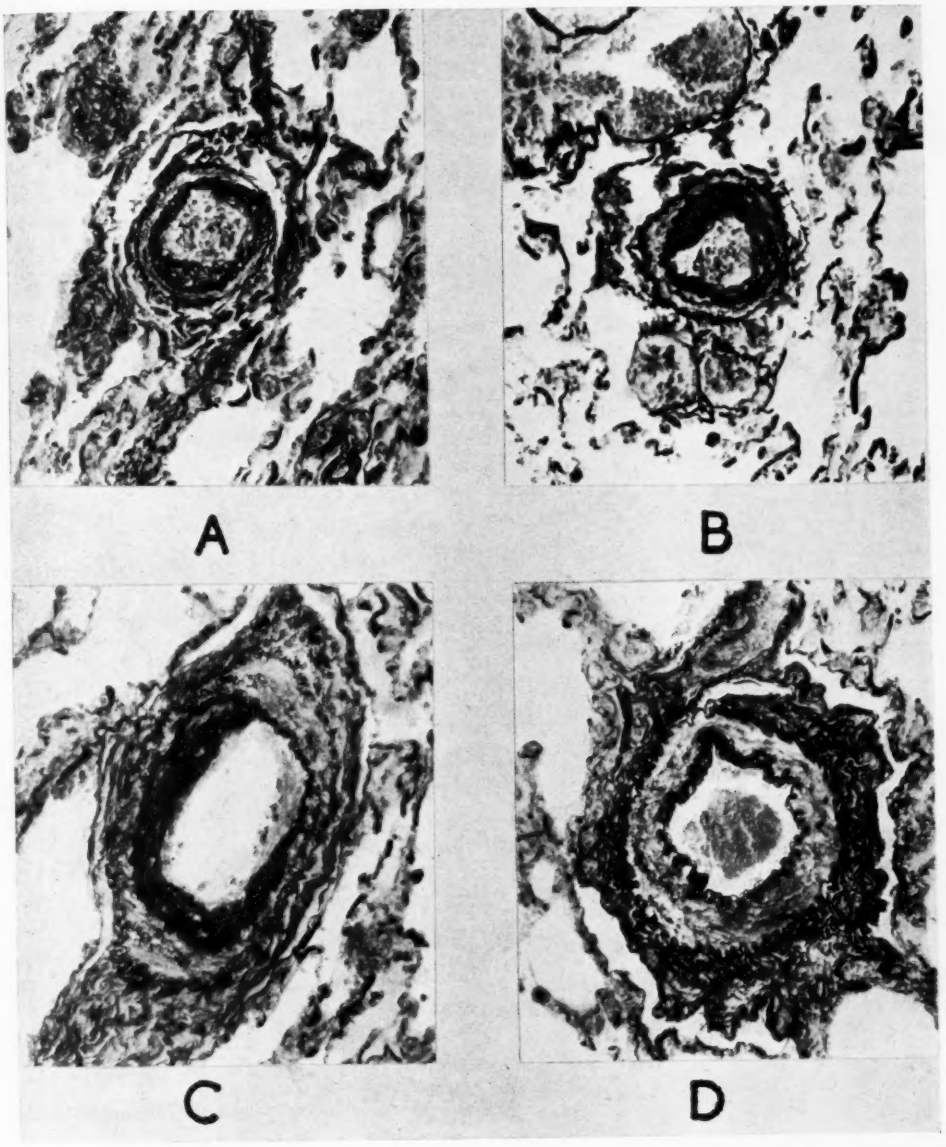

FIG. 1.—All sections from Case 4 whose pulmonary arterial mean pressure was 70 mm. Hg. All stained to show elastic by the Lawson modification of the Weigert-Sheridan method, and counterstained with van Gieson to demonstrate muscle and collagen. Magnification ×150 except in (A) where it is ×140. (A) and (B) Transverse sections of pulmonary arterioles. A distinct media is present between internal and external elastic laminæ. There is intimal proliferation of fibroelastic tissue (elastosis). (C) and (D) Transverse sections of muscular pulmonary arteries. There is adventitial fibrosis, a hypertrophied media, and prominent internal elastic membranes. In (C) there is intimal proliferation of fibroelastic tissue.

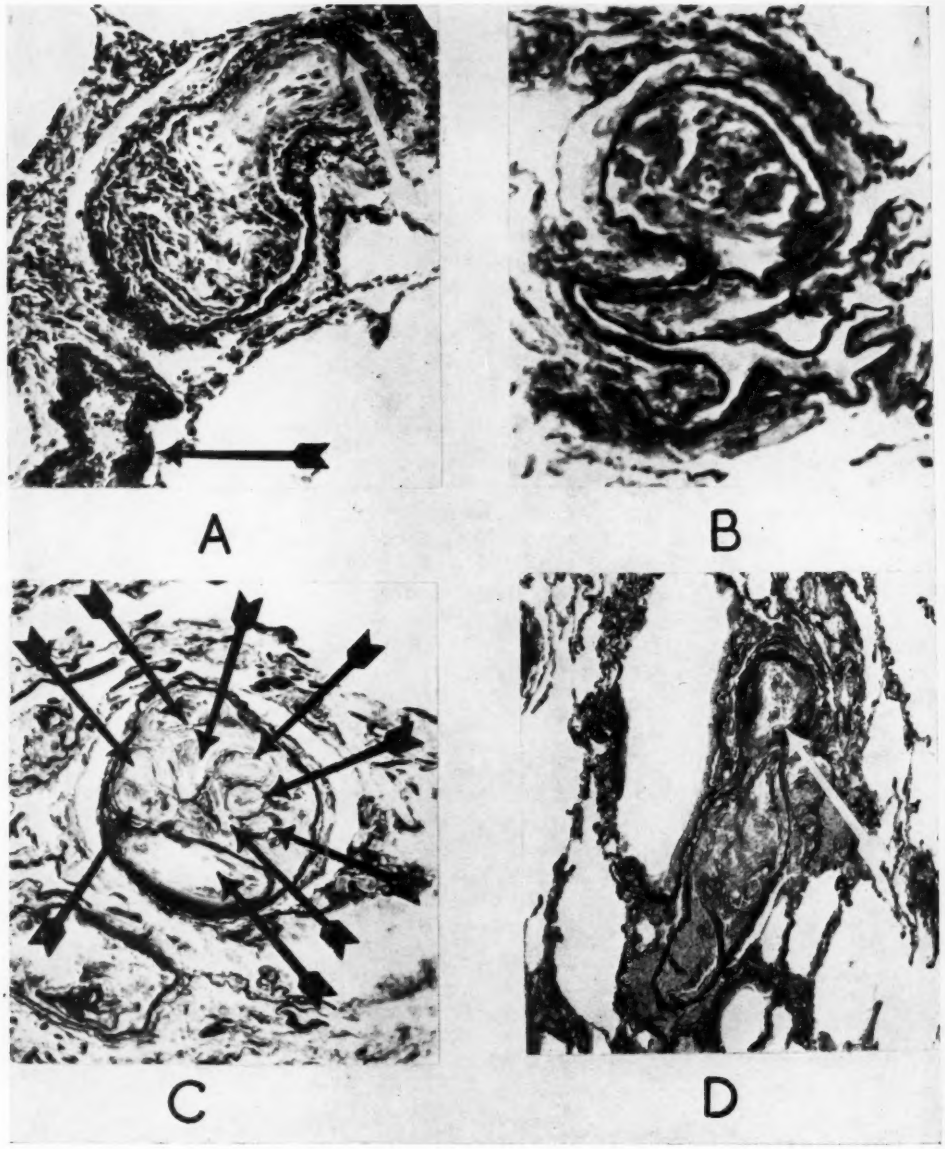

FIG. 2.—All sections stained to show elastic by the Lawson modification of the Weigert-Sheridan method, and counter-stained with van Gieson to demonstrate muscle and collagen. (A) Longitudinal section of the termination of a hypertensive pulmonary arteriole, 100μ in diameter, with distinct media between internal and external elastic laminæ, and intimal fibrosis. This vessel, indicated by a white arrow, expands abruptly to form a dilated vessel, 195μ in diameter lined by a single elastic lamina, which contains organizing blood clot. The dilated vessel narrows to give rise to a capillary indicated by a black arrow (× 150, Case 3). (B) Section through a dilated vessel similar to that described in (A). This is lined by a single elastic lamina and contains organizing blood clot. The sudden narrowing of this vessel to

a minute but there was no evidence that any of the 13 had pulmonary hypertension. Nine additional cases of atrial septal defect were thought to have had rheumatic involvement of the mitral valve also and, of these, eight had right ventricular hypertrophy and pulmonary vascular lesions. This led Welch and Kinney to conclude that cases with co-existing atrial septal defect and mitral stenosis had constant atherosclerotic changes in the pulmonary vessels. Although the authors thought that these changes were due to an increased flow of blood from the left atrium to the lungs via the right chambers of the heart following the obstruction at the mitral valve, it seems more likely that pulmonary arterial hypertension, which is known to be frequently associated with mitral stenosis was the ætiological factor.

The three patients in the present series in whom cardiac catheterization had demonstrated severe pulmonary arterial hypertension (Cases 3, 4, and 5) showed medial hypertrophy and severe intimal fibrosis in the muscular pulmonary arteries, and a distinct muscular media with two elastic laminæ and severe intimal fibrosis in the pulmonary arterioles. Evans (1951) has described similar changes in another case of atrial septal defect complicated by severe pulmonary arterial hypertension. They have been described commonly in patients in whom severely raised pulmonary artery blood pressure has been associated with Eisenmenger's complex (Stewart and Crawford, 1933; Old and Russell, 1950; Brown *et al.*, 1955), ventricular septal defect (Heath *et al.*, 1956), patent ductus arteriosus (Johnson *et al.*, 1950; Cosh, 1953; Dammann *et al.*, 1953; Hultgren *et al.*, 1953; and Whitaker *et al.*, 1955), idiopathic pulmonary hypertension (Gilmour and Evans, 1946; Branwood, 1954; Aitchison and Richmond, 1955; and Heath *et al.*, 1957), and mitral stenosis (Larrabee *et al.*, 1949; Henry, 1952; Hicks, 1953; Denst *et al.*, 1954; and Heath and Whitaker, 1955*b*). Furthermore, these vascular changes, which may be associated with pulmonary atheroma, medial necrosis confined to the blood vessels of the lung, dilatation of the branches of the muscular pulmonary arteries, and the development of bronchopulmonary anastomoses (Heath and Whitaker, 1956) appear to be associated with a clinical picture that is dominated by the clinical signs and symptoms of pulmonary arterial hypertension. The combination of these specific anatomical changes and this characteristic group of clinical symptoms and signs constitutes a distinct clinicopathological syndrome termed the pulmonary vascular obstruction syndrome by Cutler *et al.* (1954) and hypertensive pulmonary vascular disease by Heath and Whitaker (1956).

The additional histological appearances noted in Cases 3 and 4 are probably significant, for when fluid passes through a narrow channel into a dilated vessel or a large number of channels of similar diameter under a head of pressure, the flow is immediately slowed and the pressure diminished. Thus in the present case, blood at the severely raised pulmonary artery blood pressure in the muscular pulmonary arteries and pulmonary arterioles narrowed by intimal fibrosis entered dilated terminations containing numerous channels and this probably resulted in lowering of the pressure and slowing of the pulmonary blood flow at these points.

Vessels below 100μ in diameter with a distinct muscular media, such as have been described as characteristic of pulmonary arterial hypertension in a preceding paragraph, do not have the same significance when seen in the neonatal period. Civin and Edwards (1951) have pointed out that such vessels occur normally in the fœtal and neonatal period as the intralobular arteries, which are the developing muscular pulmonary arteries, and this has been confirmed by one of us (D. H.) in the examination of lungs from control infant cases (Heath, 1956). It needs to be stressed, however, that severe intimal fibrosis never occurs normally in the lung in the neonatal period and is indicative of pulmonary arterial hypertension.

Legend to Fig. 2 (continued from p. 330).

produce pulmonary capillaries is illustrated (×250, Case 3). (C) Transverse sections through another of these dilated, thin-walled terminations of hypertensive pulmonary arterioles, showing the numerous channels, indicated by arrows, in the recanalized thrombus (×140, Case 4). (D) Longitudinal section of the termination of a hypertensive pulmonary arteriole with distinct media between internal and external elastic laminæ, and intimal fibrosis. This vessel, indicated by a white arrow, expands abruptly to form a dilated vessel lined by a single elastic lamina and containing organized, recanalized thrombus (×85, Case 4).

Summary

Specimens of lung were obtained at autopsy from five patients with atrial septal defect whose pulmonary artery blood pressures had been previously recorded by cardiac catheterization. A close relationship was found between these pressures and the histological appearance of the small pulmonary blood vessels.

The pulmonary blood vessels were normal in two patients with normal pulmonary arterial pressure but increased pulmonary blood flow. In three patients with pulmonary hypertension there was medial hypertrophy and severe intimal fibrosis in the muscular pulmonary arteries (100 to 1000μ), and a distinct muscular media with two elastic laminæ in the pulmonary arterioles ($<100\mu$).

In two patients the hypertensive arterioles terminated by sudden dilatation to form thin-walled vessels that were lined by a single elastic lamina and filled by what appeared to be organizing blood clot which had undergone multiple recanalization. It is considered that such an anatomical structure is of significance in producing a local lowering of pulmonary artery blood pressure.

We are most grateful to Professor P. R. Allison, Dr. O. Brenner, and Dr. J. W. Brown for allowing us to study the autopsy material from patients who had been under their care and for allowing us access to the relevant cardiac catheterization data.

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PROGNOSIS OF ISOLATED VENTRICULAR SEPTAL DEFECTS

BY

E. MANNHEIMER, D. IKKOS, AND B. JONSSON

From the Pediatric Clinic, Karolinska Sjukhuset, Stockholm, Sweden

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The diagnosis of ventricular septal defects (V.S.D.) during life was made more reliable by the introduction of cardiac catheterization (Wood *et al.*, 1955; Kjellberg *et al.*, 1955; Selzer, 1954; Blount, 1955). The old clinical syndromes such as Roger's disease and Eisenmenger's complex do not cover all the types. One of the aims of this paper is to evaluate the severity of our cases in order to determine the prognosis and the indications for operation. The classification as well as the clinical judgment are mostly based on observations made in a previous work by Kjellberg *et al.* (1955). Their results, together with our increased experience from about 20 new cases, will form the basis for this study.

Anatomy and Hæmodynamics. The old concept that benign ventricular septal defects are located in the muscular part of the septum (low V.S.D.) and the severe ones in the membranous septum (high V.S.D.) is incorrect. The great majority are situated in the membranous septum. The size of the defect and the resistance in the two circulations determine the size and direction of the shunt and also the pressure in the lesser circulation (Selzer, 1954). If the defect is big, 1·5–3 cm. (Selzer, 1954), the pressures in both ventricles may become equilibrated. When the pulmonary resistance is low and the defect is big the left-to-right shunt will be large. With increasing pulmonary resistance the shunt will be smaller and its direction left-to-right, right-to-left, or mixed.

Material

The material consists of 72 patients, aged from 3 months to 20 years, who were admitted to our clinic from 1951 to 1955. Every case had a complete clinical examination including phonocardiography, electrocardiography, roentgenography, and cardiac catheterization. In addition in some instances angiocardiography was also performed. There was equal distribution according to sex, i.e. 35 girls and 37 boys. All cases with complicating pulmonary stenosis or other malformations were excluded from this study. Fig. 1 shows the classification of cases into three main groups, with sub-divisions (see legend to Figure). There were four deaths, all small children aged 1–2 years (Group III).

Results

In the most severe cases definite cardiac symptoms were already present in infancy. An improvement in health could often be noted after the first year of life. Physical under-development was not seen frequently. Cyanosis was noted only exceptionally. Fatigue and dyspnœa were observed in the severe cases but the great majority were without symptoms.

The physical signs within each group were surprisingly characteristic.

Group I(a). The systolic murmur was the only sign of V.S.D. This murmur was systolic in time, rather highly pitched, and it ended with a normally split second sound (Fig. 2). The murmur

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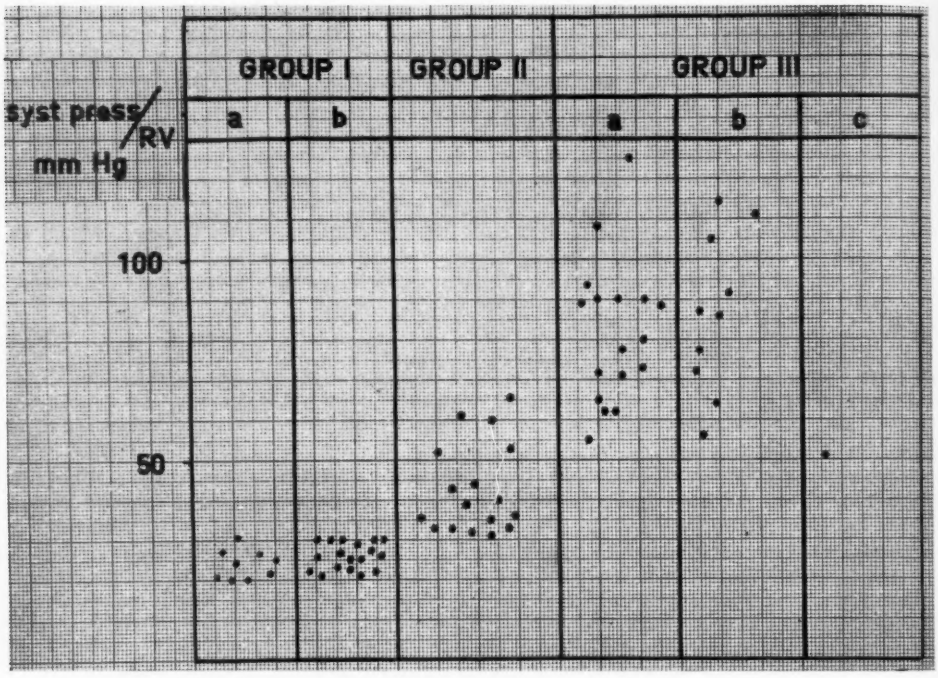

FIG. 1.—Distribution of cases in different groups of the classification.
Group I(*a*): normal pressure in the right ventricle without significant shunt on catheterization.
Group I(*b*): normal pressure and significant left-to-right shunt.
Group II: moderately elevated right ventricular pressure and left-to-right shunt.
Group III(*a*): equilibrated pressures and left-to-right shunt.
Group III(*b*): equilibrated pressures and mixed shunt.
Group III(*c*): single ventricle.

was often localized to a distinct area at the third to fourth left interspaces and it was rather sparsely transmitted to other areas. There were no signs of cardiac enlargement.

Group I(b) (normal pressure and a significant left-to-right shunt). In this group physical signs were similar to those in Group 1(*a*). However, the systolic murmur was often more intense and extended as a rule throughout systole (Fig. 3). In some cases the palpation of the apex beat showed slight left ventricular predominance.

Group II (moderately raised right ventricular pressure). In these patients a heaving cardiac impulse was often found. The systolic murmur was harsh and the second sound more accentuated with a very short interval between the aortic and pulmonary components (Fig. 4). Some of the cases also presented a faint mid-diastolic apical murmur.

Group III(a) (equilibrated pressures and left-to-right shunt). The systolic murmur was loud with a marked thrill; the cardiac impulse was heaving and a more or less pronounced præcordial bulge was present. The second sound over the pulmonary orifice was much accentuated and not clearly split (Fig. 5).

Group III(b) (equilibrated pressure and mixed shunt). In these cases the flow decreased owing to high pulmonary resistance and consequently the systolic murmur was faint but was followed by a highly accentuated second sound which was not split and which was very often palpable in the second left interspace. In a few cases there were no murmurs at all (i.e. " silent V.S.D.") (Fig. 6).

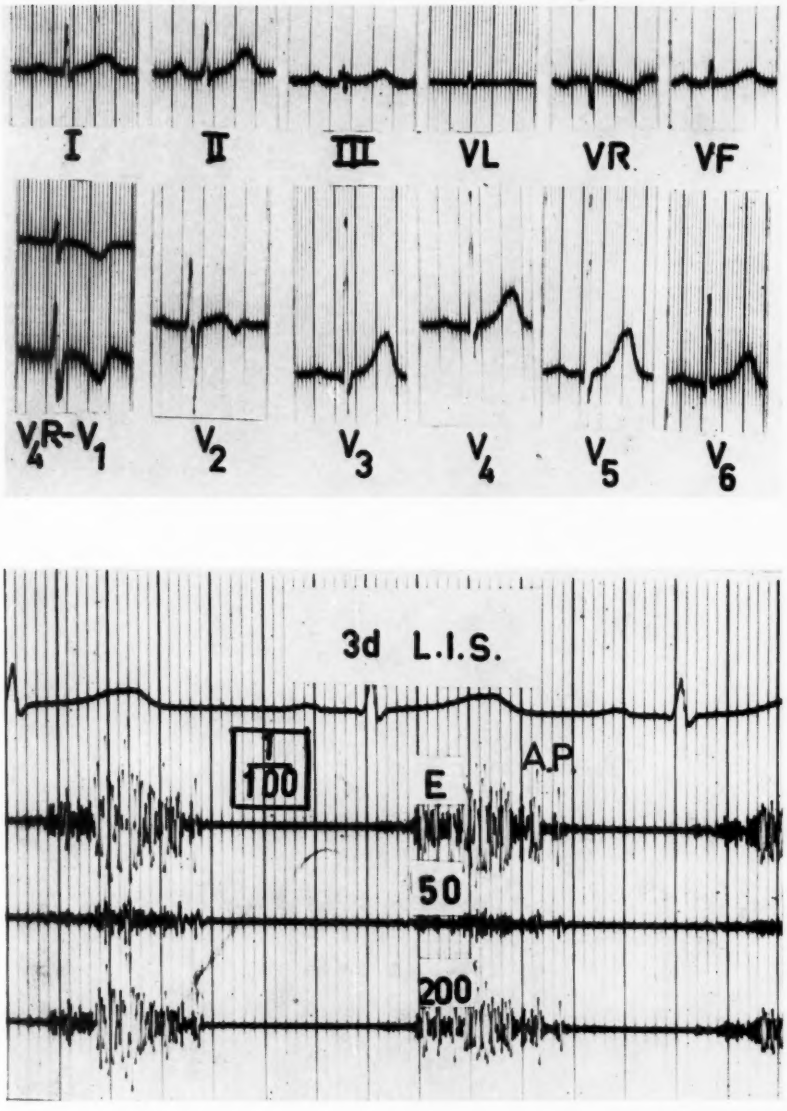

FIG. 2.—Electrocardiogram and phonocardiogram in V.S.D. with normal right ventricular pressure and insignificant shunt. Group I(*a*) (Girl, 3 years, D.S. 520805).

Normal EC. PCG reveals a high-pitched systolic murmur and a normally split second sound. A and P: aortic and pulmonary components of the second sound. E: earlike tracing. Boxed figures indicate the degree of amplification. Other figures denote standard frequencies of the filters. LIS: left intercostal space.

Pressures: mm. Hg: R.V. 20/2, P.A. 19/7.

Oxygen contents: vol. % O_2: R.A., 11·5; R.V., 11·8; P.A., 11·8.

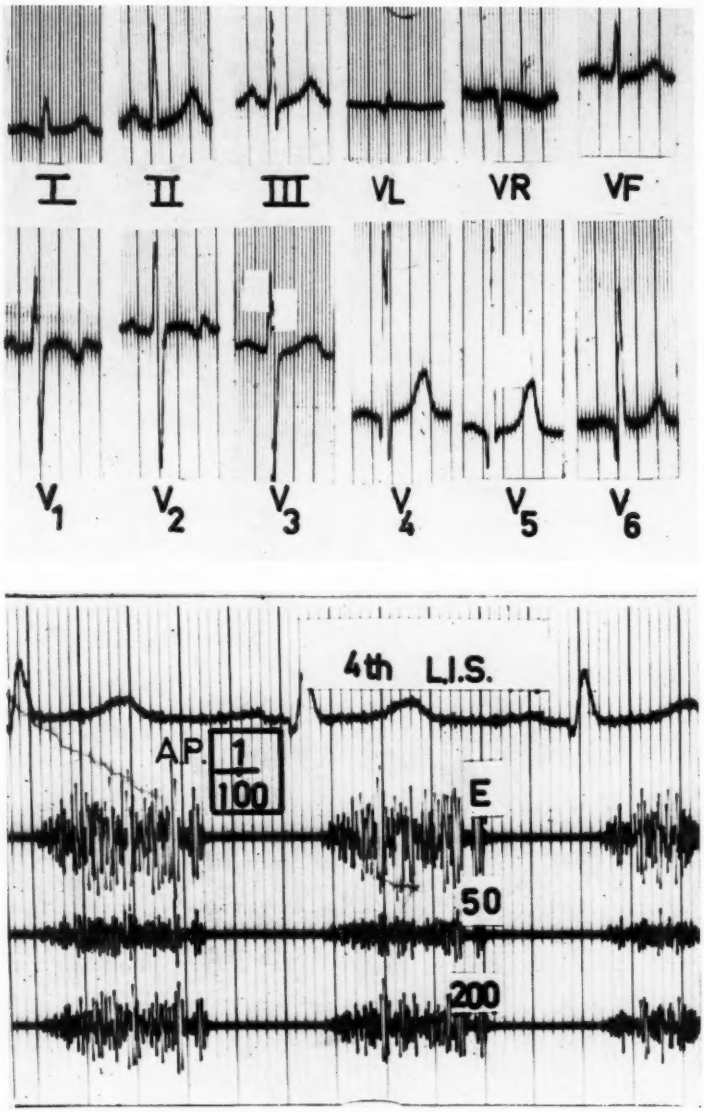

FIG. 3.—Electrocardiogram and phonocardiogram in V.S.D. with normal right ventricular pressure and significant shunt. Group I(*b*).
(Girl, 9 years, D.S. 461019).
EC shows R wave amplitude in V5 and V6 at upper limits of normal variation. Deep Q in V6. PCG shows systolic murmur of high amplitudes and normally split second sound. For explanation of signs see Fig. 2.
Pressures: mm. Hg: R.V. 22/3, P.A. 17/6.
Oxygen contents: vol. % O_2: R.A., 9·8; R.V., 12·1; P.A., 11·1

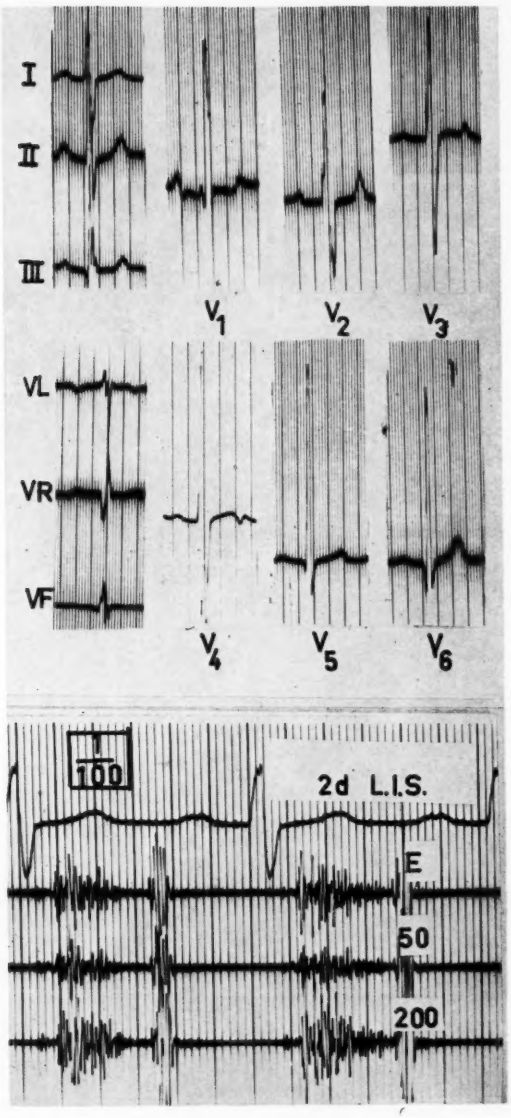

FIG. 4.—Electrocardiogram and phonocardiogram in V.S.D. with elevated right ventricular pressure and significant shunt. Group II.

(Girl, 11 years, B.J. 430527).

EC in V1 shows rsR's' pattern and in V3 and V4, high R/S. In V5 and V6 half amplitude (1 MV=½ cm.). Interpretation: Combined ventricular hypertrophy. PCG over pulmonary area shows systolic murmur and accentuated, not definitely split, second sound. For explanation of signs see Fig. 2.

Pressures: mm. Hg: R.V. 61/6, P.A. 54/28.

Oxygen contents: vol. % O_2: R.A., 10·6; R.V., 13·1; P.A., 13·1; F.A., 95% saturation.

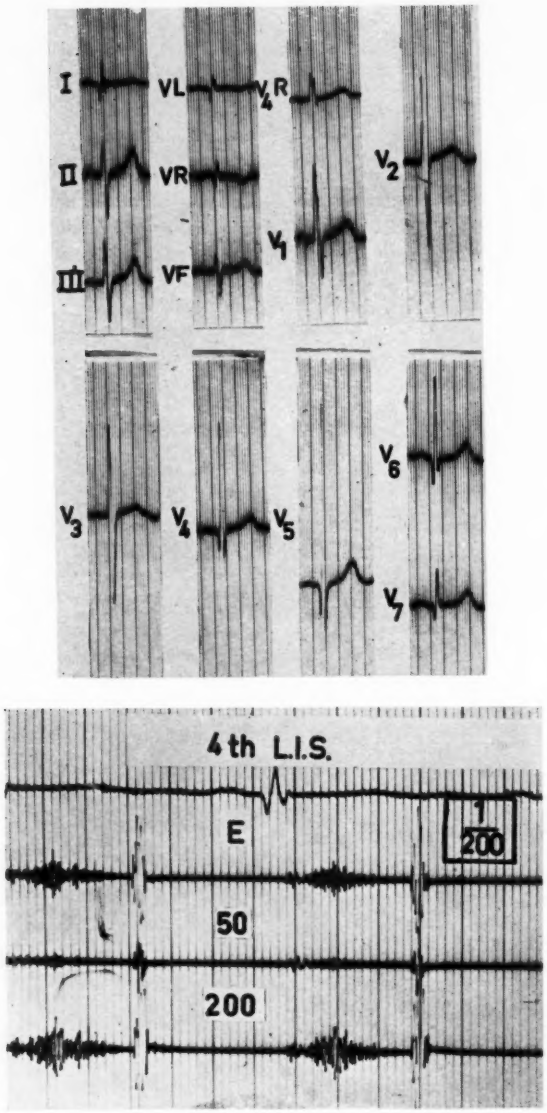

FIG. 5.—Electrocardiogram and phonocardiogram in V.S.D. with equilibrated pressures and left-to-right shunt. Group III(*a*).

(Boy, 5 years, E.H. 490114).

EC shows combined ventricular hypertrophy: RS pattern in V1: large R/S in V2 and V3 and high R waves in V5 Half amplitudes in V2, V3, and V4 (1 MV=½ cm.). PCG shows moderately loud systolic murmur and accentuated (not split) second sound. For explanation of signs see Fig. 2.

Pressures: mm. Hg: R.V. 71, P.A. 81.

Oxygen contents: vol. % O_2: R.A., 10·3; R.V., 12·5; P.A., 12·6; F.A., 91% saturation.

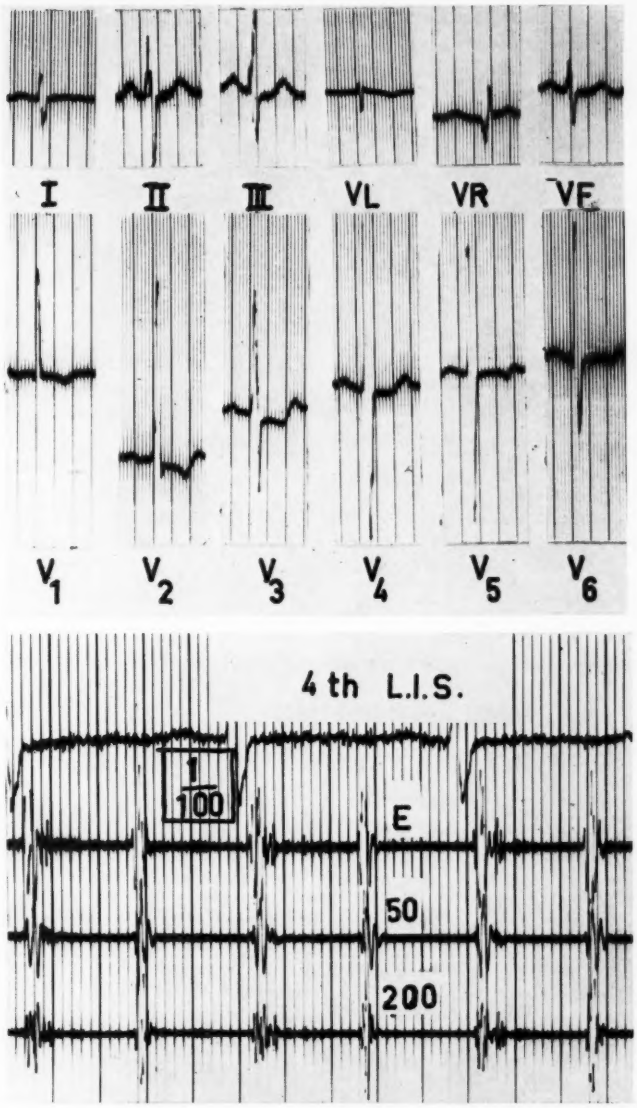

FIG. 6.—Electrocardiogram and phonocardiogram in V.S.D. with equilibrated pressures and mixed shunts. Group III(*b*).

(Girl, 3 years, T.B. 520323).

EC shows combined ventricular hypertrophy (right hypertrophy more pronounced): RS pattern in V1, large R/S in V3–V5 and qRS pattern in V6. PCG over the fourth left intercostal space shows a highly accentuated (not split) second sound. The systolic murmur is very faint (" silent V.S.D."). For explanations of signs see Fig. 2.

Pressures: mm. Hg: R.V. 91/6, P.A. 92/62.

Oxygen contents: vol. $\%O_2$: S.V.C., 11·9; I.V.C., 12·4; R.A., 12·2; R.V., 12·4; P.A., 12·1; F.A., 81% saturation.

A parasternal lift along the left sternal border was indicative of right ventricular hypertrophy. In this group are also included some cases with loud murmurs, large left-to-right shunts, and unsaturation of the arterial blood (see Catheterization).

Group III(c) (*complete mixture of the blood: single ventricle*). Only one case in this group has been observed.

It seems obvious that mild cases of V.S.D. present a normally split second sound. In pulmonary hypertension, on the other hand, the pulmonary valves close earlier and consequently the second sound is accentuated and pure. This relationship was known earlier (Wood, 1955) and it was a constant and reliable sign in our patients. Thus a split second sound was absent in 22 out of 69 cases examined phonocardiographically. In these 22 instances the pressure in the pulmonary artery exceeded 50 mm. Hg. On the other hand, in only 4 out of the remaining 37 cases with a split second sound was the pulmonary artery pressure above 50 mm. Hg.

Electrocardiography. The determination of normal electrocardiograms was made according to Ziegler (1951). Right and left ventricular hypertrophy were diagnosed according to Marsico *et al.* (1955).

The principal cardiographic changes are summarized in Table 1.

TABLE I

ELECTROCARDIOGRAMS IN 72 CASES OF V.S.D.

Group	No. of cases	Normal	Abnormal	Auricular enlargement and hypertrophy			Incomp. A-V block (grade I)	Ventricular hypertrophy		
				Right only	Left only	Combined R+L		Right only	Left only	Combined R+L
I(*a*)	9	8	1				1			
I(*b*)	18	12	6		2		1		6	
II	17	6	11		1	1	4	—	3	7
III(*a*)	17	—	17	5	6		3	2	1	14
III(*b*)	10	—	10	6	2		1	2	—	8
III(*c*)	1	0	1		1			—	1	—
Total	72	26	46	11	12	1	10	4	12	29

In Group I(*b*) one-third of the cases showed left ventricular hypertrophy (Fig. 3). In Group II the incidence of left ventricular hypertrophy was higher and it was often combined with right ventricular hypertrophy (Fig. 4). The cardiograms in Group III were all abnormal with signs of ventricular hypertrophy (Fig. 5 and 6). A deep Q wave in V6 and high amplitudes of the R/S pattern in V2–V4 were noticed in most of the abnormal electrocardiograms (Fig. 3–6).

One case of auricular flutter was observed. Left atrial enlargement was present in 13 cases with large left-to-right shunts. Right atrial hypertrophy was seen in 12 cases with pulmonary hypertension. Finally, 10 cases of incomplete A-V block (Grade 1) were found.

Roentgenologic Examination. Kjellberg and Rudhe (1955) have published a detailed description of the radiological and angiocardiographic findings, so only a short summary of their observations need be given here.

In cases with normal right ventricular pressure the X-ray appearance was on the whole normal. With increased flow and right ventricular pressure the heart became enlarged; there was increased pulsation in the pulmonary artery and its branches and the left atrium was dilated. Left atrial enlargement was of diagnostic value as it indicated the presence of the shunt below the level

of the atria. With increased resistance in the lesser circulation the peripheral vessels of the lungs were often narrow, the right ventricle became enlarged, and was seen in the lateral view to bulge against the thoracic wall. When hypertrophy of the left ventricle was present it could seldom be demonstrated radiologically.

In *cardiac catheterization* blood gas analyses and pressure determinations were of high diagnostic importance and the classification given above was based upon the hæmodynamic findings (Fig. 1).

Passage of the catheter through the defect was rarely successful. When the aorta was reached it was often difficult to judge if the catheter had passed through the defect or directly into the overriding aorta. Except in Group I(*a*) the blood gas analyses were decisive for the diagnosis. However, difficulties were encountered. In some cases of atrial septal defect a higher oxygen content was found in the right ventricle than in the right atrium, probably due to a failure to get a good mixed sample in the right atrium. In some cases of V.S.D. a higher oxygen content was noted in the outflow tract of the right ventricle and even in the pulmonary artery. All these difficulties must carefully be taken into consideration. The systolic pressure in the right ventricle is shown in Fig. 1. It will be seen that there are patients in Groups II and III with about the same right ventricular pressures, i.e. between 50 and 70 mm. Hg systolic. This depends on the fact that some of those belonging to Group III were young babies and children and consequently had a relatively low systemic pressure.

In Fig. 7 is shown the correlation between the pressure in the lesser circulation and the difference in oxygen content between the pulmonary artery and right atrium, i.e. the size of the left-to-right shunt. It can be seen that a clear-cut shunt may be present without any increased pressure. In Groups II and III (elevated pressure and left-to-right shunt) the pressure increases on the whole with increased shunt. The correlation was highly significant ($p<0{\cdot}001$). In Group III(*b*) (equilibrated

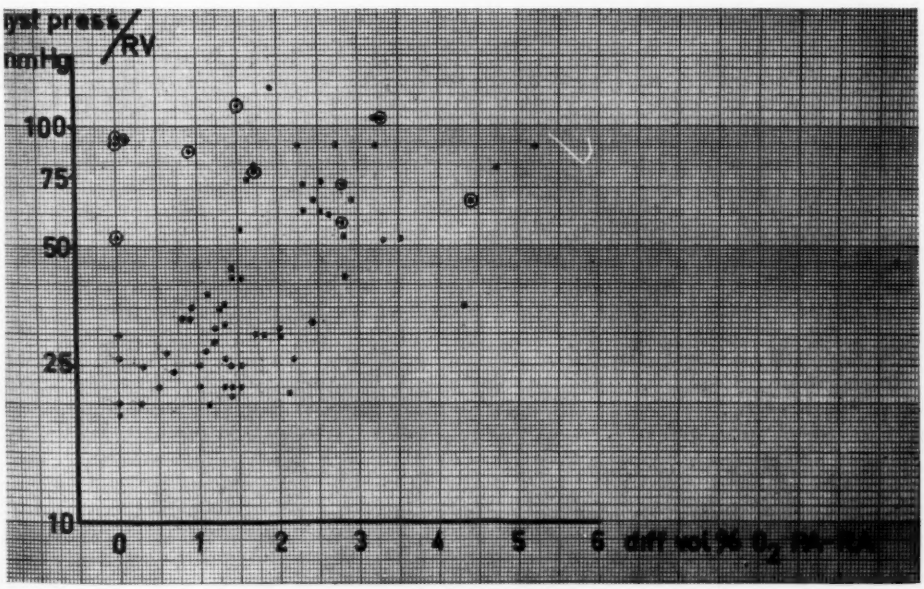

FIG. 7.—Correlation of the size of the left-to-right shunt (O_2 diff. P.A.–R.A.) with the right ventricular pressure.
● =cases belonging to groups I, II, and III(*a*).
⊙=cases belonging to group III(*b*).

pressure and mixed shunt) there was no correlation between the systolic pressure in the right ventricle and the size of the shunt. There are cases without any left-to-right shunt (silent V.S.D.), some other instances with a slight shunt, and finally a small group of patients with a large shunt into the right ventricle. These latter cases have been classified in Group III(*b*) because they showed unsaturation of their arterial blood. Some of these patients may have had impaired pulmonary oxygen diffusion—a view that has been criticized by other authors (Selzer, 1951, 1954). However, unsaturation of pulmonary venous blood has been shown to exist in both atrial and ventricular septal defects in small children (Jonsson, 1955). In some cases the defect is located between the left ventricle and the infundibular part of the right ventricle (so-called infundibular septal defects). As the roots of the aorta and the pulmonary artery are placed closely to each other with one common outflow tract good pre-requisites are present for a mixed shunt.

Angiocardiography. Direct visualization of the defect by rapid injection of contrast medium into the right ventricle was impossible if the systolic pressure there was below 50 mm. Hg. Injection from the left ventricle could only rarely be done and injection from the left atrium gave no information owing to dilution of the contrast medium.

In cases with equilibrated pressure and especially in cases in which murmurs were absent or very faint, and in which left-to-right shunts were small or insignificant, angiocardiography was often the key to the diagnosis (see below).

Discussion

The clinical diagnosis of isolated V.S.D. does not offer any great difficulties when the systolic pressure in the right ventricle is not equilibrated, i.e. Groups I(*a*), I(*b*), and II. An infundibular stenosis, either isolated or combined with V.S.D., is the only other malformation giving a similar clinical picture. The phonocardiogram may be valuable as a pathologically split second sound (Mannheimer *et al.*, 1954, and Kjellberg *et al.*, 1955) is usually present in infundibular stenosis in addition to the cardiogram showing right ventricular hypertrophy. The withdrawal pressure curve from the pulmonary artery through the infundibular chamber into the right ventricle is also characteristic. Finally, selective angiocardiography will show the anatomical details.

The cases belonging to Group III can be confused with two other conditions, namely, atypical patent ductus arteriosus and primary pulmonary hypertension. Clinically these differentiations are extremely difficult. Cardiac catheterization and angiocardiography give the correct answer.

The question arises as to the possibility of judging the prognosis from the findings on examination in the different classification groups.

According to the present classification (Fig. 1) the severity of the disease increases progressively from Group I to Group III. Functional disturbances are absent or minimal in Group I while in Group III such changes are pronounced. Our findings suggest that information about the severity might also be gained from clinical data, phonocardiography and electrocardiography. A loud systolic murmur and a normally split second sound together with a cardiogram that is either normal or showing only slight left ventricular hypertrophy speak in favour of a V.S.D. that has not yet produced any significant circulatory disturbances. On the other hand a faint murmur with a second sound accentuated but not split, and a clearly abnormal cardiogram are characteristic of rather severe hæmodynamic changes. So it seems reasonable to assume that the prognosis in patients belonging to Group III is poor and that it is rather good in those of Group I. The outlook in Group II is intermediate.

The only correct way to make a real prognostic study of our 72 cases is a sufficiently long follow-up. As this pre-requisite was not available we tried an alternative method. We studied 14 records with a suspected diagnosis of V.S.D. These belonged to patients, who were admitted to the Norrtull's pediatric clinic, Stockholm, 20–25 years ago. At that time the diagnosis was made by auscultation. Of these 14 cases one died of brain tumour: the heart was normal. One case was a combination of atrial septal defect and mild

valvular pulmonary stenosis. Another was a typical case of tetralogy of Fallot. Two cases—19- and 20-year old women—had ventricular septal defects with normal pressures in the right ventricle: both were included in this study in Group I(*b*). The remaining ten cases were all re-examined by us recently. All showed normal auscultatory findings, normal cardiograms and phonocardiograms and were diagnosed as healthy subjects. This follow-up study showed that the diagnosis of congenital heart disease was highly uncertain 20 years ago. Physiological systolic murmurs were often classified as representing congenital heart disease.

From other quarters (Engle, 1954; Edwards, 1954) it has been pointed out that the mortality in V.S.D. during the first year of life is high. After this age the prognosis is said to be better. Our four deaths were all small children aged one to two years and classified in Group III. One of them, a boy of nearly two years died after attempted intracardiac operation. The remaining three had large hearts, were dyspnœic even at rest, and died during acute attacks of upper respiratory infection. The pathological findings were as follows: (i) an infundibular septal defect, (ii) a large defect in the membranous septum, and (iii) a large defect in the muscular septum (this one-and-a-half-year-old boy had auricular flutter during life). These three cases all represent large defects situated in three different parts of the septum. They support the opinion that the size of the defect rather than its localization is of prognostic significance (Kjellberg *et al.*, 1955; Selzer, 1954).

It has been claimed that the pulmonary resistance has a tendency to increase with age in cases with V.S.D. and large shunts (Blount *et al.*, 1955). On the other hand Wood (1955) stated that a " high pulmonary resistance does not develop slowly over the years but is determined at or shortly after birth." We have not been able to recatheterize our patients after an interval of several years, so our findings do not permit any final conclusions. In the present material were included five patients between 16 and 20 years of age where the systolic pressures in the right ventricle were below 32 mm. Hg, showing that there was no increased pulmonary resistance.

During recent years intracardiac surgery has been introduced, but few operations on V.S.D. have been performed up to the present time. The question arises as to which cases are suitable for surgical treatment. In view of the very great risks that still exist no patients without pulmonary hypertension should be operated on (Group I and Group II without pronounced hypertension). It seems reasonable that cases with large left-to-right shunts and increased pulmonary artery pressure but without high resistance (partially Group II and III) ought to be chosen for surgical treatment.

Summary

The findings on clinical examination and catheterization in 72 cases of isolated ventricular septal defect are presented.

Patients with V.S.D. but without pronounced hæmodynamic changes showed (*a*) a loud systolic murmur over the third left interspace; (*b*) a normally split second sound; and (*c*) a normal electrocardiogram or slight left ventricular hypertrophy.

Severe cases of V.S.D. were characterized clinically by the following features.

(*a*) The second sound is highly accentuated over the second left interspace, and not split.

(*b*) The murmur may be loud throughout systole but there are instances of " silent V.S.D." with a very faint systolic murmur or no murmur at all. These latter represent high pulmonary resistance with a small shunt.

(*c*) The cardiogram in these cases is characterized by signs of combined left and right ventricular hypertrophy alone. In addition, both left and right auricular hypertrophy are observed in some of these patients.

A positive correlation was found between the systolic pressure in the right ventricle and the magnitude of the left-to-right shunt in all cases except those with equilibrated pressures and mixed shunts.

The question of prognosis on the basis of the present clinical and laboratory investigations is dicussed.

When surgery has progressed so far as to make intracardiac operations free of great risk, patients with large left-to-right shunts but without high pulmonary resistance should be chosen for surgical treatment.

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AORTIC ORIGIN OF THE RIGHT PULMONARY ARTERY

BY

COLING CARO,* VICTOR C. LERMANDA, AND HAROLD A. LYONS

From the Department of Medicine, College of Medicine at New York City, State University of New York and the Kings County Hospital Center, Brooklyn, New York

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The anomalies of the pulmonary arterial circulation have been reviewed (Findlay and Maier, 1951) and classified according to the major vessel of the systemic circulation from which the anomalous vessel originates. This classification does not give recognition to the presence or absence of vascular connections between the affected lung and the lesser circulation. We have found eight reported cases (Table I) of anomalous blood supply to one lung via a single systemic artery arising directly from the aorta, proximal to the origin of the left subclavian artery. In each the normal ipsilateral pulmonary artery was absent. This paper reports one further case.

Case Report

A 23-year-old man was referred to hospital with a diagnosis of patent ductus arteriosus. His chief complaints were hæmoptysis for two years, and progressive shortness of breath on exertion for one year. A cardiac murmur had been detected at the age of four months. At seventeen years he became aware of shortness of breath on exertion and was advised to have cardiac surgery, but he refused. At no time had he been cyanosed. Hæmoptysis had occurred on more than 50 occasions; (1–2 teaspoons of bright red blood admixed with whiteish-yellow sputum) particularly after physical exertion or in the morning on waking. He was able to walk several miles on the flat but became dyspnœic after climbing two flights of stairs. There was no history of cardiac irregularity or failure.

There was no parental consanguinity and had been no maternal illness during the pregnancy. Delivery was normal and at full term. The patient was the third of nine children. Two siblings died of respiratory infections during the first few months of their lives, and a third died of bronchopneumonia at the age of one year: he was diagnosed clinically as having a cardiac anomaly but there was no necropsy.

Physical Examination

The patient was well nourished, and well developed. There was no cyanosis and no clubbing of the fingers or toes. The pulse rate was 80 a minute; the rhythm was regular. The blood pressure was 130/60 mm. Hg. The jugular venous pressure was not raised.

The trachea was in the midline; the chest excursion was bilaterally symmetrical and examination of the lungs by percussion and auscultation revealed no abnormality.

The maximum cardiac impulse was palpable in the left fifth intercostal space in the mid-clavicular line. The second pulmonic sound was palpable, and there was a faint systolic thrill in this area. There was a loud machinery murmur of maximal intensity in the second left intercostal space, also audible in the third. A diastolic murmur was heard in the fourth left intercostal space; it was not known whether this was the diastolic component of the machinery murmur or a separate murmur.

There were no other abnormal physical findings. The blood count and urine analysis were normal. In the electrocardiogram there were prominent R waves in all leads and deep S waves in V2–5—findings indicative of biventricular hypertrophy.

The postero-anterior roentgenogram of the chest (Fig. 1) showed the right hemithorax to be smaller than the left, with slight displacement of the heart to the right. The left border of the heart was prominent, suggesting left ventricular enlargement. There was also prominence of the pulmonary artery segment and

*Now at the Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania, Philadelphia.

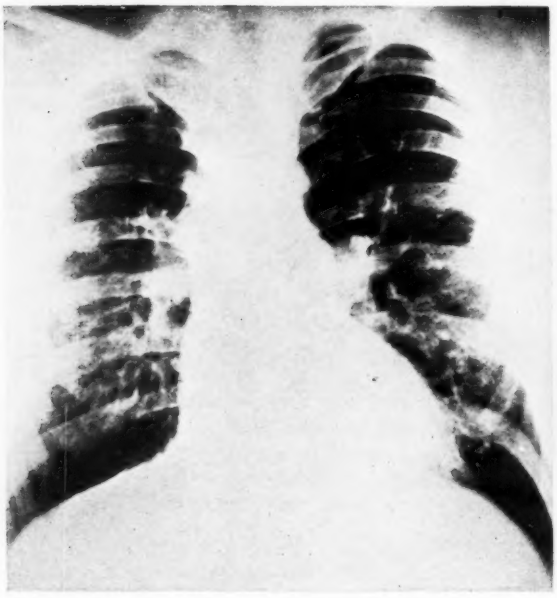

FIG. 1.—P.A. radiogram. The right root shadow is slightly higher than the left. There is prominence of the pulmonary artery segment and of the left border of the heart. The right hemithorax is smaller than the left.

FIG. 2.—Angiocardiogram in the R.A.O. position. The anomalous right P.A. is seen to arise from the posterior aspect of the ascending aorta, close to the commencement of the arch (see inset).

slight widening of the superior mediastinum. The lung fields appeared normal but both the right and the left pulmonary artery shadows were somewhat enlarged. The right root shadow was approximately 3 cm. higher than the left. On *fluoroscopy* there appeared to be moderate enlargement of the left ventricle, but no enlargement of the left atrium.

Angiocardiography was performed using the method of Robb and Steinberg (1938). In the postero-anterior position, the film exposed at 2 seconds (Fig. 3A) showed slight enlargement of the right atrium and ventricle, a normal pulmonary outflow path, and great dilatation of the main pulmonary artery. Only the left pulmonary artery and its branches were opacified and these vessels were considerably dilated.

The right pulmonary artery became opacified at 8 seconds contemporaneously with the aorta (Fig. 3B). It appeared to arise from the ascending aorta and to have no connection with the main or left pulmonary arteries. The anomalous artery seemed to displace the superior vena cava slightly laterally in its course to the hilum of the right lung. Proximally its calibre was somewhat greater than that of a normal pulmonary artery, but distally its branches were considerably narrowed.

Angiocardiography was repeated in the right anterior oblique position (Fig. 2). The vessel to the right lung again opacified with the aorta. It appeared to arise from the posterior aspect of the ascending aorta at the beginning of the aortic arch. The ductus arteriosus was not demonstrated. There was no evidence of reversal of flow in the ductus—simultaneous opacification of the descending aorta and the pulmonary artery, without opacification of the ascending aorta (Gasul *et al.*, 1953).

The size and site of origin of the vessel to the right lung made it likely that it was an anomalous pulmonary artery, and not a bronchial vessel. The right pulmonary veins became opacified on later films and appeared to pass towards the left atrium.

Bronchography. The arrangement of the bronchi was normal. There were a few areas of

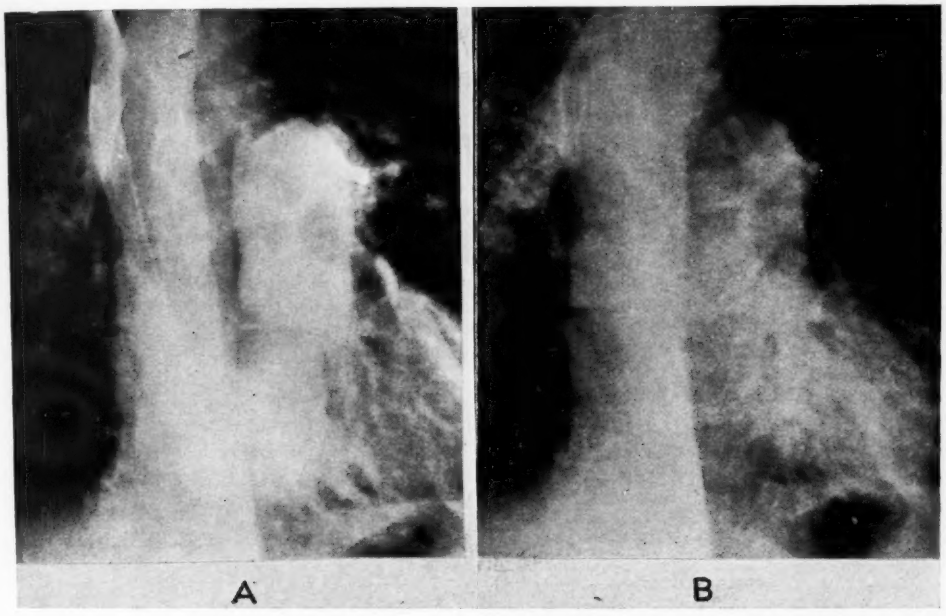

FIG. 3.—Angiocardiograms. (A) At 2 sec. the main P.A. is considerably dilated; only the left P.A. is opacified. (B) At 8 sec. the right P.A. appears to arise from the ascending aorta and has no connection with the main P.A.

slight cylindrical bronchial dilatation in the left lower lobe. It was considered unlikely that this minimal bronchiectasis was responsible for the hæmoptyses.

Cardiac Catheterization. Repeated attempts to pass the catheter into the right pulmonary artery were unsuccessful. The blood oxygen saturation in the left pulmonary artery was 14 per cent higher than in the right ventricle. The right ventricular pressure was 57/8 mm. Hg. The pressure in the left pulmonary artery was 57/33, and 75/39 mm. in the region of the ductus. The pulmonary arteriolar resistance was raised to 570 dynes cm^{-5}.

The blood oxygen saturation was 60 in the right atrium and 68 per cent in the right ventricle. This difference was interpreted as due to either slight pulmonary insufficiency (Cournand, 1949) or to a small left-to-right shunt via a ventricular septal defect. The oxygen saturation of systemic arterial blood was 96 per cent. The right ventricular output was calculated to be 4·0 and the total pulmonary flow 7·4, indicating a left-to-right shunt of 3·4 litres a minute.

In order to confirm that there was no reversal of flow in the ductus the oxygen saturation of left brachial and femoral arterial blood was determined with the patient at rest, during exercise, and after breathing 10 per cent oxygen. During exercise only, the saturation of the femoral artery sample was 2·2 per cent lower than that of blood in the brachial artery. This was not considered significant of reversal of the shunt.

Pulmonary Function Studies. There was no disturbance of combined ventilation. On bronchospirometry the right lung contributed only 39 per cent of the tidal volume. When room air was supplied to both lungs, the right did not participate in oxygen uptake although there was some elimination of carbon dioxide.

These observations are similar to those recorded by other workers in patients (Madoff *et al.*, 1952; Roh *et al.*, 1949) and in experimental animals (Bloomer *et al.*, 1949), where one lung was

perfused solely by systemic arterial blood. They were considered to have confirmed the angiocardiographic and catheterization findings that the normal right pulmonary artery was absent and that the right lung received its blood supply via an anomalous systemic artery from the aorta. When pure oxygen was supplied to both lungs, 26 per cent of the O_2 uptake was by the right. (Unfortunately the arterial O_2 saturation at this time was not estimated). This was interpreted as indicating that the right lung was capable of function under conditions of increased oxygen tension.

Surgical Treatment

Surgery was undertaken for the following reasons. (1) There was a history of progressive exertional dyspnœa. (2) There was no significant evidence of reversal of flow in the ductus arteriosus and its closure was considered advisable. (3) Intrapulmonary hæmorrhage has been reported in similar cases (White, 1950; Ambrus, 1936) and the history of recurrent hæmoptyses was regarded as an important consideration for interrupting the systemic arterial supply to the right lung. (4) The right lung had been demonstrated to be capable of gas exchange under certain conditions. It was hoped that a functional lung might result if its vascular tree were anastomosed to the lesser circulation.

Operative Procedure. The chest was entered via a long trans-sternal incision through both third intercostal spaces. The arrangement of the arteries arising from the aortic arch was normal. The ductus arteriosus was in the usual position and measured about 1 cm. in diameter and 2 cm. in length. It was manually occluded for two minutes and since this was well tolerated, with a 10 mm. Hg rise in the diastolic pressure, it was divided. No thrill was palpable anywhere after occlusion of the ductus.

The right side of the ascending aorta was then explored. The artery that had been demonstrated by angiocardiography was found in its predicted location, at the start of the arch of the aorta, and about 3 cm. proximal to the origin of the innominate artery (Fig. 4A). The anomalous vessel measured about 1·5 cm. at its point of origin but was narrowed by an abrupt funnel-shaped kinking to a diameter of 0·5 cm., with a post-stenotic dilatation to a diameter of 3 cm. The anomalous vessel was clamped next to the aorta and the proximal stump was closed. The stenotic portion was resected.

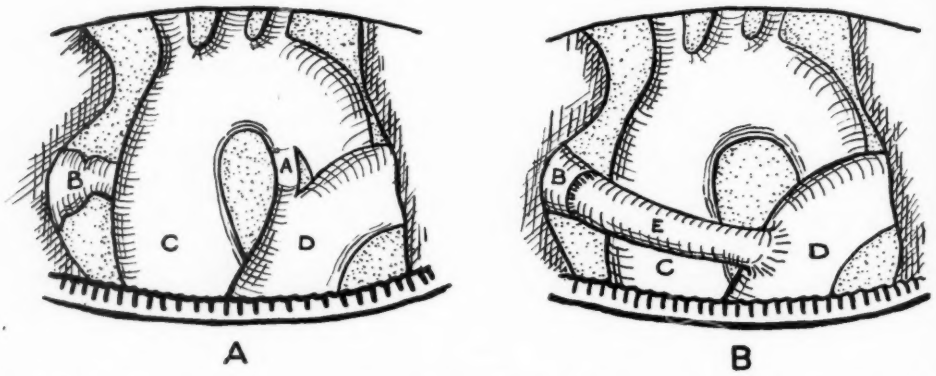

FIG. 4.—(A) The appearance at thoracotomy. (B) After division of the ductus arteriosus and completion of the anastomosis. A=ductus arteriosus; B=anomalous right P.A.; C=ascending aorta; D=main pulmonary artery ; E=anastomosis of anomalous vessel to main P.A.

An Ivalon graft was anastomosed end-to-end to the right pulmonary artery and the proximal end of the graft was swung into position anterior to the superior vena cava and ascending aorta. An end-to-side anastomosis was made between it and the main pulmonary artery about 5 cm. proximal to the site of origin of the ductus arteriosus (Fig. 4B). Pulsations were felt in the graft after the clamps were removed and there appeared to be good pulmonary blood flow into the right and left lungs. Biopsies were taken from the middle lobe on the right lung and from the lingula.

The patient regained consciousness immediately after the chest had been closed. Despite blood replacement and intravenous nor-adrenalin his blood pressure did not rise above 90 mm. and he died suddenly

about five hours after the completion of the operation. Cardiac massage was unsuccessful. All vascular closures and anastomoses were intact but the left pleural space contained about 1000 ml. of blood and there was a large hæmatoma in the left chest wall. The intrathoracic bleeding had apparently come from a lacerated intercostal artery. Permission for necropsy was refused.

Pathological Report on the Biopsies of the Right and Left Lungs. The broncho-alveolar and interstitial structure of the lung was equally well formed in both subpleural biopsy fragments and there was no alteration in the structure or distribution of capillaries in either biopsy. In the right lung small muscular arteries and some arterioles showed moderate concentric fibromuscular medial thickening and marked eccentric fibroelastic intimal thickening. Elastic laminæ were multiplied and markedly frayed. These changes especially involved bronchiolar vessels and were slight in arterioles near respiratory bronchioles and in subpleural vessels (Fig. 5A). Arteries and arterioles in the left lung showed only equivocal endothelial and muscular thickening (Fig. 5B).

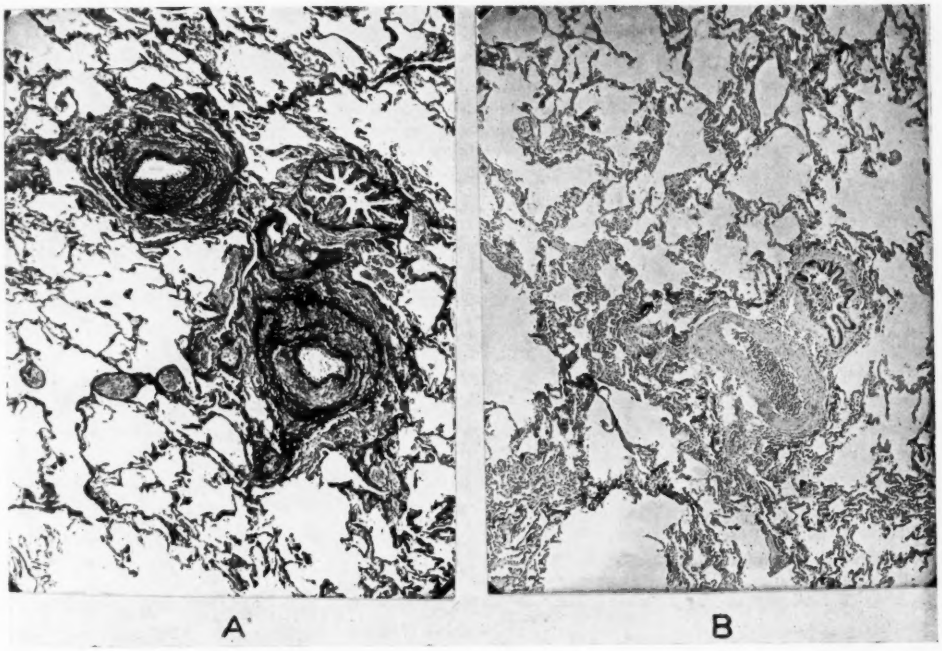

FIG. 5.—(A) Biopsy of the right middle lobe. × 32. (B) Biopsy of the lingula. × 32.

DISCUSSION

Embryology. The developmental anomaly responsible for aortic origin of a main branch of the pulmonary artery is not clearly established. In the human embryo at about 5 mm., the truncus ridges grow to fuse in the midline and divide the truncus arteriosus into the aorta and pulmonary artery. The sixth aortic arches, the precursors of the two main branches of the pulmonary artery, arise from the dorsal aspect of the truncus arteriosus, close to the mid-sagittal plane.

The abnormality may be a consequence of asymmetric origin of one of the sixth aortic arches from the truncus arteriosus (Fig. 6A) or an asymmetric anlage of one of the truncus ridges (Fig. 6B). The former theory appears probable in our case. Asymmetry of the aortico-pulmonary septum is likely to be associated with an over-riding aorta and hypoplasia of the pulmonary artery, with

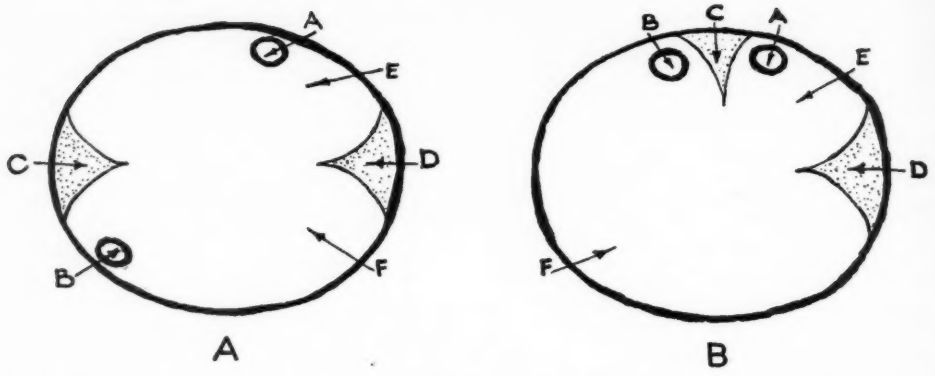

FIG. 6.—(A) Schematic representation of assymetric origin of right sixth aortic arch. (B) Schematic representation of assymetric origin of right truncus ridge. A=future left pulmonary artery; B=future right pulmonary artery; C=right truncus ridge; D=left truncus ridge; E=future main pulmonary artery; F=future aorta.

the additional possibility of a ventricular septal defect. These anomalies were not thought to be present.

Atresia of the proximal connection of the right sixth aortic arch and persistence of its distal connection to the dorsal aorta might explain anomalous origin of the right pulmonary artery. Under these circumstances the anomalous vessel might be expected to arise from the right subclavian artery. Several instances of this have been recorded (Findlay and Maier, 1951).

Review of Similar Cases. The cases we have selected (Table I) conform to one of the categories suggested by Findlay and Maier. In each there was a single anomalous artery to one lung which originated from the aorta proximal to the origin of the left subclavian artery. In addition, however, in every instance the normal ipsilateral pulmonary artery was absent. We believe that their classification should be modified to give recognition to this further abnormality. The vascular anomaly is potentially correctable. But these cases pose a problem which is not present where there is a dual circulation to the lung—that of determining whether the peripheral vascular connections are consistent with gas exchange.

In none of the eight cases was there any characteristic physical finding. A feature of interest in ours was a slight reduction in the size of the hemithorax on the side of the anomalous artery. This has been reported in patients with absence of a main branch of the pulmonary artery (Madoff *et al.*, 1952; Flynn *et al.*, 1954).

Cyanosis was recorded in four cases; but was only present from birth in one where the transverse aortic arch was absent and the descending aorta received its blood supply from the ductus arteriosus. Cyanosis was reported terminally in the other three, two of whom appear to have died of pneumonia.

Life expectancy appears to be poor for six of the eight cases died within the first few months of life. There was, however, pathological evidence of pneumonia in three: the use of antibiotics may improve the prognosis, but pneumonia developing in the only functioning lung must have grave consequences.

A congenital cardiovascular anomaly was known to be present in all but one case. Findlay and Maier observed that there were significant associated cardiovascular anomalies in 75 per cent of cases where the origin of the anomalous pulmonary vessel from the systemic arterial system was above the level of the lung roots, but in only 16 per cent of those where the abnormal pulmonary vessel arose below this level.

The most common additional anomaly was a patent ductus arteriosus. Including our own

TABLE I

CASES OF AORTIC ORIGIN OF ONE PULMONARY ARTERY WITH ABSENCE OF NORMAL IPSILATERAL PULMONARY ARTERY

Author	Age and sex	Clinical history	Physical signs	Necropsy findings		
				Anomalous vessel, origin and diameter	Associated anomalies	Lungs
Fraentzel, 1868	25 yr. F	Progressive dyspnœa and œdema for 6 mo.	Kyphoscoliosis, cyanosis, large heart. Murmurs—apical P.S.M., lt. parasternal S.M. and D.M.	Rt. P.A. from aorta close to start of arch. 2 finger breadths	Aortico-pulmonary septal defect	Collapse of basal segments of rt. lower lobe
Thomas, 1941	3 mo. F	Cough and fever for 3 days	Dyspnœic and cyanosed. Loud S. and D.M.	Lt. P.A. from transverse aortic arch, to left of left innominate. Size not recorded	Rt. aortic arch; absent ductus; absent pulm. valve; V.S.D.; potentially P.F.O.	Broncho-pneumonia
Bopp, 1949	7 mo. F	Dyspnœic from birth	Markedly enlarged heart. Loud S.M. over all valve areas	Rt. P.A. from ascending aorta. 0·6 cm.	P.D.A.; vessels from transverse aorta, proximal to distal, rt. carotid, lt. carotid, lt. subcl., rt. subcl.; vascular ring	Lt.: congestion and œdema Rt.: Increased peri-arterial connective tissue
Sikl, 1952	4 mo. M	Cough and fever, 6 days, murmur since birth	Râles throughout left lung. Loud apical S.M.	Rt. P.A. from ascending aorta. 0·5 cm.	None	Lt.: Pneumonic consolidation Rt.: Structure normal, patchy consolidation
Sikl, 1952	Stillborn, full term Sex not recorded			Lt. P.A. from ascending aorta. 0·3 cm.	V.S.D.; overriding aorta; rt. aortic arch; reversal of main cranial branches; bicuspid pulm. valve; absent ductus	Lobar anatomy normal. Lungs atelectatic
Jew and Gross, 1952	53 hr. M	Cyanosis from birth	Systolic murmur	Rt. P.A. from ascending aorta. 3·5 cm.	P.F.O.; V.S.D.; absent transverse aortic arch; P.D.A.	Not reported
Maier, 1954	4 mo. F	Cyanosis and dyspnœa	Large heart, S.M., râles at bases	Rt. P.A. from ascending aorta. 2·7 cm.	P.F.O.; lt. common carotid from innominate artery	Pneumonia and irregular hæmorrhagic areas, both lungs
White, 1950	*Alive* aet. 32 yr. F	Hæmoptysis 8 years, especially after exertion. Murmur since age 3 years	Heart not enlarged, pulmonic second sound accentuated. Loud apical P.S.M.	*X-rays.* Prominent P.A. and hilar shadows. Area of increased density in lt. peripheral lung field. *Operative findings.* Lt. P.A. from aortic arch. Lt. upper lobe resected. Hæmorrhage into lung substance, apparently from rupture of an atheromatous branch of the anomalous vessel.		

case, this lesion was present in three of the six cases with anomalous right pulmonary artery, possibly a significant association. One of the remaining cases with a right-sided lesion had an aortico-pulmonary septal defect. The ductus was absent in two of the three cases where the anomaly was on the left.

Diagnosis. Hæmoptysis occurring after exertion may be significant. The conventional radiogram of the chest is likely to be normal, although there was slight elevation of the right root shadow in our case. At present it would appear that angiocardiography provides the only means of detecting this rare anomaly. Cardiac catheterization and bronchospirometry supplied confirmatory evidence and permitted study of the disturbed physiology.

Physiology. We considered that the limited gas exchange observed on the right side, when our patient breathed 100 per cent oxygen, was consistent with a normal alveolar capillary relationship. Moreover, he did not become cyanosed after the anomalous artery was anastomosed to the pulmonary circulation. This probably indicated that the right lung began to contribute to oxygen uptake and was not functioning as a veno-arterial shunt. Differential diffusion studies were not performed, but might have enabled us to assess better the functional potential of the right lung.

Summary

Aortic origin of the right pulmonary artery was diagnosed by angiocardiography in a patient with patent ductus arteriosus. Confirmatory procedures were performed and surgical correction attempted.

The reported cases are reviewed and a modification of the method of classification suggested. The high incidence of associated patent ductus arteriosus is noted.

We are indebted to Dr. M. M. Newman for the surgical aspects of the case, to Dr. V. Bleisch for the pathological report, and to Dr. G. Talbert of the Department of Embryology.

Drs. Garrett, Shibuya, and Pereyma assisted us with the translation of references. The patient was referred to us by Dr. Fontanetta of Greenpoint Hospital.

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PULMONARY VASCULAR PATTERNS IN PULMONARY HYPERTENSION

BY

A. E. DOYLE, J. F. GOODWIN, C. V. HARRISON, AND R. E. STEINER

From the Departments of Medicine, Morbid Anatomy, and Radiology, Postgraduate Medical School of London and Hammersmith Hospital

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The radiological appearances of the pulmonary vascular system in mitral stenosis with pulmonary hypertension have been reported previously (Goodwin *et al.*, 1952; Davies *et al.*, 1953). In mitral stenosis with much pulmonary hypertension arterial narrowing was demonstrated on plain X-ray films and on pulmonary arteriograms, in the lower zones and sometimes in the mid zones of the lungs.

This paper reports further studies of the pulmonary vascular pattern in mitral stenosis, and also in certain types of congenital heart disease with pulmonary hypertension.

Methods and Selection of Patients

Patients were studied by plain radiography of the chest, pulmonary arteriography or venous angiography, and cardiac catheterization. The radiographic material previously reported in mitral stenosis (Davies *et al.*, 1953) has been used to compare the appearances with those of 20 cases with congenital heart disease in whom the pulmonary arterial systolic pressures were 70 mm. Hg or more: all but 3 had right-to-left shunts. There were 8 patients with atrial septal defects, one patient with a single atrium, 5 patients with ventricular septal defects, one patient with atrial and ventricular septal defects and total anomalous pulmonary venous drainage, and 5 with patent ductus arteriosus, two of whom had reversed their flow. The chest radiographs were also examined of 15 patients with left-to-right shunts but pulmonary artery systolic pressures of less than 60 mm. Hg.

In addition, 30 cases of mitral stenosis and 6 cases of congenital heart disease have been studied by post-mortem pulmonary arteriography and by histological examination of the pulmonary arteries in various parts of the lung. The post-mortem pulmonary arteriograms were prepared by the following method.

The lungs were dissected out complete with their main arteries. After removing all post-mortem clot, the arteries were cannulated and all air bubbles removed under water. Formol-saline was then run through (about 1 litre of 15% per lung) to ensure satisfactory fixation. The lungs were then injected with a mixture of barium sulphate and gelatine usually at a pressure of 80 mm. Hg; if the pulmonary artery pressure in life was known to have been higher than this, they were injected at the known pressure. When injection was complete the cannulae were clamped and the lung distended by running formol-saline into the bronchi. The bronchi were not tied and the lungs were allowed to assume their normal size. They were then placed in iced water to set the gelatine and stored in formol-saline until fixation was complete (a minimum of 14 days). Details of the apparatus and the injection mass have been published elsewhere (Harrison and Wood, 1949). After radiographs of the whole lung had been taken, the lung was divided up into segments and further radiographs taken of the following segments: middle lobe or lingula, anterior upper lobe, apical upper lobe, apical lower lobe, posterior basal, anterior basal. These segments were subsequently cut in 5-mm. slices from hilum outwards at right angles to the main artery and histological sections taken at known levels.

In most cases both lungs were studied, but in some only one, the other being either unsuitable or kept for other purposes. No difference was found between right and left lungs in respect of their vessels.

As in the group with mitral stenosis, there was dilatation of *the main pulmonary arteries* in all

Control lungs were treated in a similar way, both sexes and various ages being examined. It was, therefore, possible to compare radiographs and histological sections with those of controls of roughly corresponding ages.

Radiological Studies

(*a*) *Mitral Stenosis*

The cases reported here include those reported as Grade II pulmonary hypertension by Davies *et al.* (1953), the systolic pulmonary artery pressures being 70 mm. of mercury or above. All patients had considerable dilatation of the main pulmonary arteries and main branches, and much narrowing of the smaller peripheral arteries in the lower and mid zones. Narrowing of the small peripheral arteries was never seen in the upper zones. Other changes were the occurrence of horizontal lines in the lower zones towards the periphery of the lung field in the costophrenic angles (Shanks and Kerley, 1951; Fleischner and Reiner, 1954). There was also a diffuse haziness in the lower zones. The appearances seen in the plain films were confirmed angiographically in those cases in which this investigation was performed (Fig. 1 and 2).

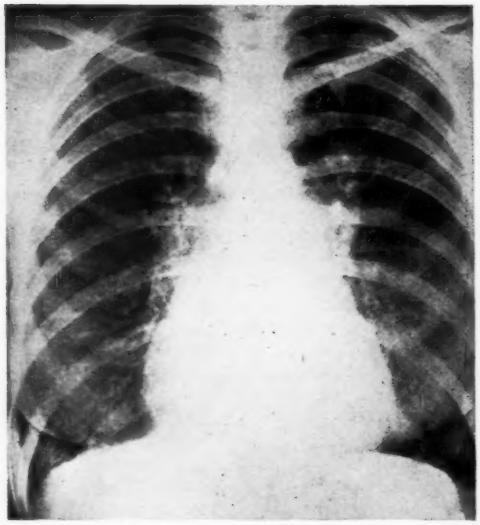


Fig. 1.—Severe pulmonary hypertension due to mitral stenosis. There is considerable enlargement of the main pulmonary arteries, with irregularity and narrowing of the peripheral arteries in the lower zones. The arteries to the upper zones, however, are not reduced in calibre. Faint costophrenic lines are also present.

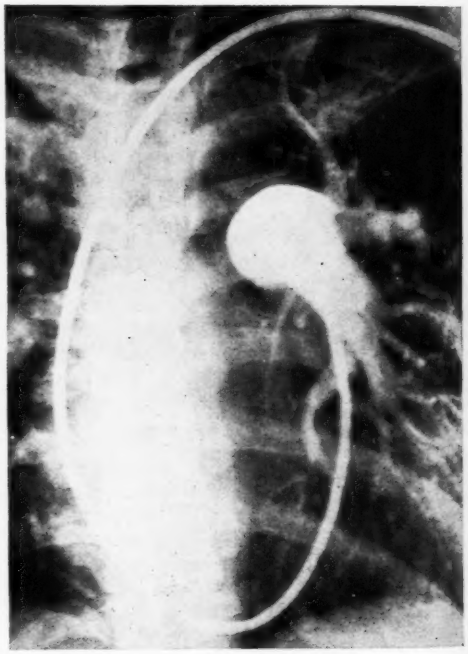


Fig. 2.—Left pulmonary arteriogram in severe pulmonary hypertension due to mitral stenosis. The left main pulmonary artery is greatly enlarged, but the medium-size branches to the lower zones are narrowed, in contrast to those in the upper zone.

(*b*) *Congenital Heart Disease with Pulmonary Hypertension*

The systolic pulmonary artery pressures ranged from 70 to 150 mm. Hg. Sixteen patients had some clinical cyanosis, due to reversal of the shunts. The following changes were noted in plain films and in angiocardiograms.

As in the group with mitral stenosis, there was dilatation of *the main pulmonary arteries* in all patients. In two of these, both with reversed patent ductus arteriosus, the dilatation was moderate: in the remaining 18, it was extreme.

In contrast to the findings in mitral stenosis, *the medium-sized arteries* both to the lower zones and the upper zones were larger than normal in 18 of the 20 patients studied. In the remaining 2 patients, one of whom had a ventricular septal defect, and the other, a patent ductus with totally reversed flow, the medium-sized branches were of normal size.

In 10 patients, *the small peripheral arteries* appeared to be of normal or larger than normal size and distribution. In the remaining 10, the small peripheral arteries were narrower than normal or were not visible. As with the changes in the medium-sized arteries, the changes were evenly distributed throughout both upper and lower zones. There was no relationship between the peripheral arterial changes and the magnitude of the shunts present.

The costophrenic horizontal lines, which were frequently seen in mitral stenosis, were noted in only 3 of the 19 subjects studied. The diffuse haziness in the lower zones encountered in those with mitral stenosis, was not seen in any of the congenital group (Fig. 3, 4, 5, and 6).

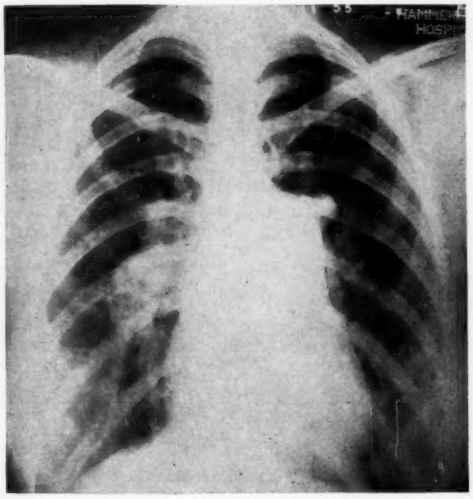


FIG. 3.—Atrial septal defect with bi-directional shunt and severe pulmonary hypertension. Shows enormous enlargement of main pulmonary artery and branches, and oligæmia of the peripheral lung fields present equally in upper, mid, and lower zones. The large pulmonary arteries showed marked intrinsic pulsation on fluoroscopy.

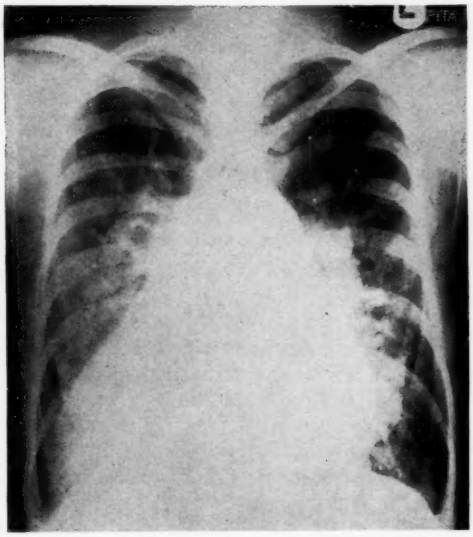


FIG. 4.—Single auricle. Dextrocardia. Bi-directional shunt. Severe pulmonary hypertension. There is enormous enlargement of the pulmonary arteries, and the small branches appear well filled out to the periphery.

(c) *Congenital Heart Disease without Severe Pulmonary Hypertension*

Examination of this group revealed essentially similar changes to those seen in the hypertensive group in that all had enlargement of the main and medium-sized arteries. Two patients, however, had oligæmia of the periphery of the lung, similar to that seen in the hypertensive group, and in one patient obvious costophrenic lines were seen.

While oligæmia at the periphery of the lung usually indicated reduction in, or reversal of, the left-to-right shunt due to increased vascular resistance, this was not always the case, and it was

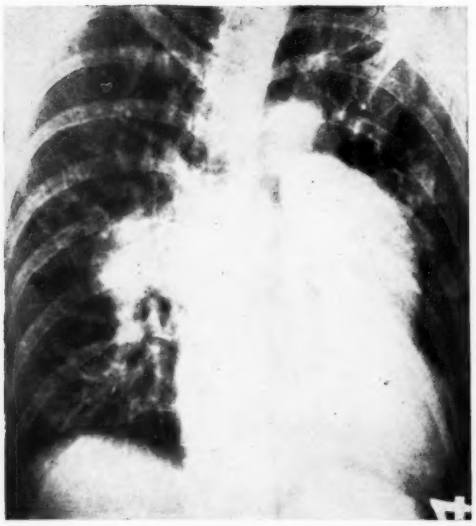


FIG. 5.—Angiocardiogram of ventricular septal defect with severe pulmonary hypertension and right-to-left shunt, showing great enlargement of the large pulmonary arteries, but deficient filling and narrowing of the peripheral branches in both upper and lower zones. Early filling of the aorta from the right ventricle can be seen.

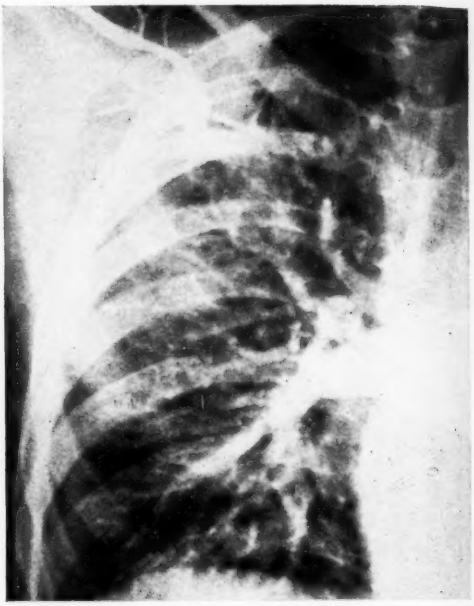


FIG. 6.—Angiocardiogram of ventricular septal defect with severe pulmonary hypertension and right-to-left shunt. The large pulmonary arteries are greatly enlarged, but the small branches are of normal size. No peripheral oligæmia.

not possible to determine the presence or absence of severe pulmonary hypertension on examination of the chest film except when the hypertension was very severe.

Fig. 3 shows the chest film of a patient with an atrial septal defect. Her systolic pulmonary arterial pressure was 90 mm. Hg, and there is great enlargement of the main and intermediary branches and peripheral oligæmia. By contrast, Fig. 4 shows the chest film of a patient with dextrocardia and single atrium, whose pulmonary artery systolic pressure was identical, yet no peripheral oligæmia can be seen. In Fig. 7, however, there is peripheral underfilling in a child with an atrial septal defect whose pulmonary artery systolic pressure was normal, and the left-to-right shunt large. Fig. 5 and 6 contrast the appearances in two patients with severe pulmonary hypertension.

The Effects of Hypotensive Agents upon the Pulmonary Circulation

(*a*) *Mitral Stenosis.* We have found (Davies *et al.*, 1954) that hexamethonium can reduce the pulmonary arterial pressure in severely hypertensive patients without a significant fall in cardiac output or systemic arterial pressure, suggesting a specific effect upon the pulmonary vasculature. We have recently extended these studies, and have found that the fall in pulmonary vascular resistance may be greater than the systemic, even in cases with mild pulmonary hypertension. These results will be reported fully later.

(*b*) *Congenital Heart Disease.* Seven patients with shunts and severe pulmonary hypertension have been given hexamethonium or tolazoline during cardiac catheterization. Six had bi-directional

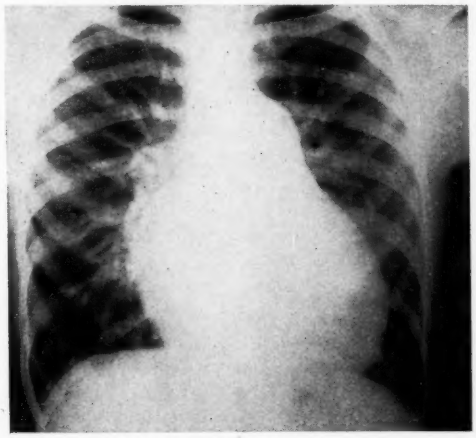


FIG. 7.—Atrial septal defect, but no pulmonary hypertension. The main pulmonary arteries are enlarged, but the medium sized branches are normal, and there is apparent underfilling of the small branches producing peripheral oligæmia.

shunts with severe pulmonary hypertension, and one had severe pulmonary hypertension, but no right-to-left shunt.

In three patients there was no fall in pressure, in two it was slight, and in the remaining one, moderate (but associated with a comparable fall in cardiac output).

The ready fall obtained in cases of mitral stenosis with comparable levels of pulmonary hypertension was never seen. The results of this study are not yet complete and will be reported in full elsewhere.

POST-MORTEM PULMONARY ARTERIOGRAPHY

(*a*) *Mitral Stenosis*

Arteriograms technically suitable for assessment were available in 30 cases. The pulmonary artery pressure had been measured in life in 15 and the systolic pressure was greater than 70 mm. Hg in 8 of them.

Plain films during life had shown pulmonary hypertensive changes in 19 cases; the remaining films could not be assessed for various reasons such as the presence of hæmosiderosis, pulmonary œdema, or infarction.

In assessing post-mortem arteriograms certain arbitrary divisions of position and size were made. It was found that different groups of segments had different appearances and that the grouping did not correspond with the anatomical lobes. Thus, the middle lobe or lingular arteries behaved like lower lobe ones and arteries of the apical segment of the lower lobe behaved like upper ones. We shall, therefore, refer to upper and lower zone arteries and not to the lobes. Also, for convenience we shall refer to arteries of the following groups of size: main pulmonary arteries, segmental arteries and their primary divisions, small arteries (down to about 0·5 mm. lumen diameter), and background (arteries too fine to be seen clearly individually). In assessing the size of the pulmonary arteries, each case was compared with controls of similar age and lung size.

The following changes were noted in the arteriograms.

Main pulmonary arteries. In 13 cases the main right or left pulmonary artery was enlarged, but in 17 cases there was no significant difference from the controls.

Segmental arteries and their primary branches. In this group the upper and lower zone arteries were different in appearance and they will therefore be considered separately. The upper zone arteries were enlarged in 11 cases and some of these were slightly tortuous; they were of normal size in 18 cases and slightly narrowed in one case. The lower zone arteries on the other hand were enlarged only in 2 cases, were of normal size in 14, narrowed in 12, and could not be assessed owing to emboli in 2 cases. In this group of arteries, those of the upper zone were usually enlarged or normal while those of the lower zone were normal or narrowed, consequently there was a difference in the size of the arteries of the two zones, the upper being the larger, in 19 cases.

Small arteries. These showed much the same changes as the larger branches but with a greater zonal difference. In the case of the upper zone arteries, 10 cases showed enlargement, 16 were of normal size, and 4 were narrowed. In the lower zone arteries one case only showed enlargement, seven were of normal size, and 19 were narrowed; three could not be assessed owing to multiple emboli. Of the 27 cases that could be assessed, 23 showed a difference in arterial calibre between the two zones. Background filling was diminished in 22 cases and normal in 8. In 16 of the 22 cases with diminished filling the lower zone was less well filled than the upper.

The vascular narrowing so far considered has always been a regular narrowing affecting all of a group of vessels equally. In some cases, however, a different type of focal narrowing was seen. It affected individual arteries, nearly always in the group of segmental or their first divisions, irregularly along their length and to a very severe degree. In all such cases only arteries of the lower zone were affected. This type of narrowing was proved to be due to atheroma and generally of great severity. It was seen in 12 out of the 30 cases and it was closely correlated with the presence of thrombotic or embolic arterial occlusion. Ten cases showed thrombo-embolic occlusion and in 8 of these there was focal narrowing in the other arteries.

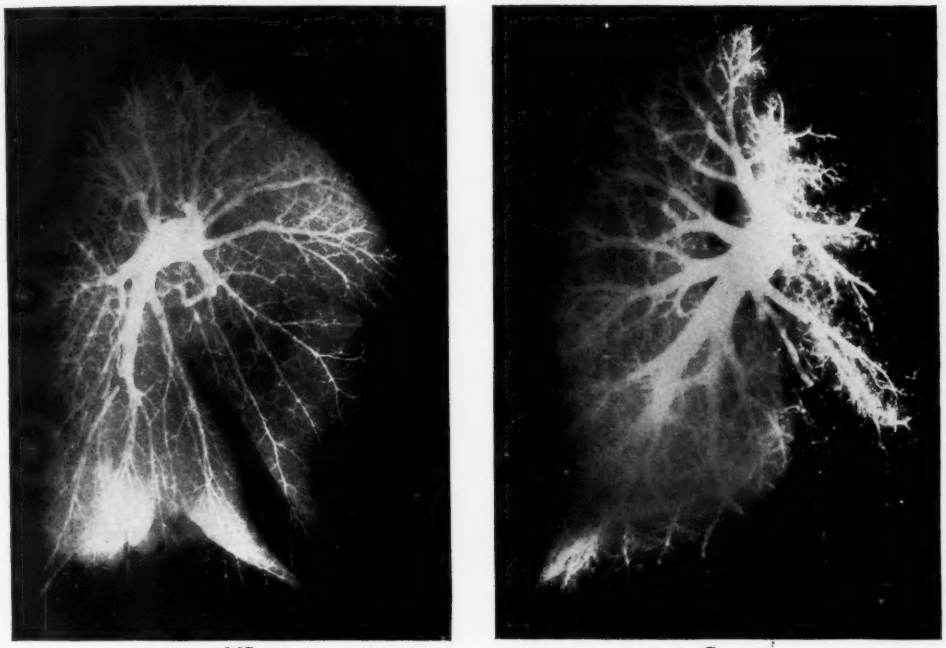
Fig. 8 shows an arteriogram of a case of mitral stenosis paired with a control of similar age and lung size for comparison. There is striking narrowing of the primary segmental, medium, and small branches confined to the lower zones.

(*b*) *Congenital Group*

In this group 4 cases of atrial septal defect, one case of single atrium, and one case of patent ductus arteriosus were available for post-mortem examination. In four of these full investigation with angiography was carried out; in the other two the lungs were obtained after a necropsy elsewhere and only ordinary dissection and histology were possible. Since the findings in these two cases were the same as in the four injected cases we feel justified in including them. In the four cases in which the systolic pulmonary artery pressure was measured it was grossly raised (70–128 mm. Hg), and in life all had shown marked dilatation of the main pulmonary arteries, and major branches, with reduction in size of the fine peripheral arteries. This reduction was equally distributed throughout the lung, so that there was oligæmia of the peripheral lung fields in all zones. In one of the cases examined by dissection only, the systolic pulmonary artery pressure had been 90 mm. Hg and in the other 40 mm. Hg.

In all 6 cases the main pulmonary arteries were dilated, moderately in four and enormously in two. The segmental arteries and their primary branches were dilated in all cases. This was enormous in three and in the other three as great as in any of the mitral cases. In all there was accompanying tortuosity. The dilatation was equally severe in the upper and the lower zones and unlike the mitral groups, no difference could be detected.

The smaller arteries could only be estimated in the four injected cases. In all these the second divisions of the segmental arteries were a little enlarged but with further divisions the arteries very rapidly diminished in size so that most small arteries were narrowed. The background filling was minimal in all cases. As in the case of the larger arteries and in contrast to the mitral cases there was no difference between the upper and lower zones.



MS C

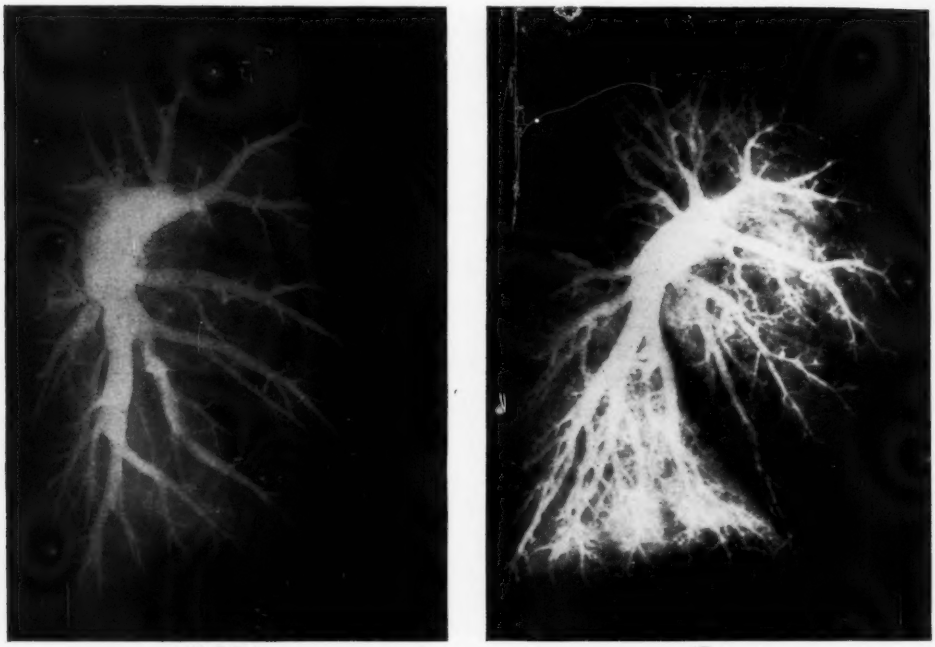
FIG. 8.—Post-mortem pulmonary arteriogram in a case of mitral stenosis (MS), compared with a control (C). There is narrowing of the primary segmental, medium, and small-sized pulmonary arteries confined to the lower zones.

None of these cases showed atheromatous narrowing, either in the arteriograms or on subsequent dissection. Fig. 9 shows the appearances in a patient with an atrial septal defect who had severe pulmonary hypertension in life, compared with a control of similar age and lung size. There is great tortuosity and enlargement of the pulmonary arteries extending down to the medium-sized branches, but there is striking reduction in " background " filling which is distributed equally throughout all zones of the lung (see also Fig. 3).

MACROSCOPICAL DISSECTION

(*a*) *Mitral Stenosis.* The changes in vascular size noted in the radiographs were confirmed. The two types of narrowing, focal and diffuse, were found to correspond to two different processes. The ordinary diffuse narrowing seen in the lower zones was due to uniform thickening of the artery, apparently by contraction. The focal narrowing was due to intimal plaques of atherosclerosis bulging into the lumen and narrowing it locally. Minor degrees of atherosclerosis were present in most cases but these did not encroach on the lumen sufficiently for any changes to be detectable in the radiographs or on dissection. Thrombotic or embolic occlusions with corresponding infarcts, old or recent, were present in 10 cases.

A feature that became apparent on dissection of the injected and uninjected lungs was the curious distribution of congestion and œdema. These both showed a tendency to localize in the central and upper parts of the lungs. In the ordinary case with death in congestive failure this distribution was discernible but not obvious. It was obvious in cases of acute cardiac failure with



(A.S.D.) (C)

FIG. 9.—Post-mortem pulmonary arteriogram in atrial septal defect (ASD) with severe pulmonary hypertension, compared with a normal control (C) of similar age and lung size. There is great enlargement and tortuosity of the pulmonary arteries extending down to the small branches, but there is loss of background filling due to involvement of the very small arteries, which is equally distributed in upper and lower zones.

pulmonary œdema. In such cases there was extreme congestion of the central and upper zones with œdema and little of either in the lower zones (Fig. 10). This peculiar distribution has been described by Jackson (1951) and was also noted in uræmia by Doniach (1947).

(*b*) *Congenital Group.* There was no evidence of atheromatous narrowing on dissection of the pulmonary arterial tree.

HISTOLOGY

(*a*) *Mitral Stenosis.* Two processes were seen in the arteries, hypertrophy and atherosclerosis. The former was seen at all levels. It could only be estimated with certainty by comparing the thickness of the vessel wall with that of an exactly corresponding artery from a control lung. The degree of hypertrophy varied between the upper and lower zones, the latter always being the greater. In some cases this difference was of minor degree, in others it was considerable (Fig. 11A). This hypertrophy affected only the media and was totally independent of any intimal thickening that was present. Intimal thickening occurred as atherosclerosis to some degree in most cases. It showed exactly the same distribution as the hypertrophy, affecting the lower zones. In the majority of cases it took the form of fatty infiltration of a slightly thickened intima and affected only segmental arteries or their primary divisions. Such intimal thickening had no effect on the lumen and was comparable with the superficial fatty streaking of the aorta of young people. Severe atheroma, of the type seen in peripheral arteries in the greater circulation, occurred in a minority.

FIG. 10.—Photograph of left lung in patient with mitral stenosis and severe pulmonary hypertension who died in pulmonary œdema. The congestive changes are confined to the central and upper zones, and are absent from the bases.

In 13 out of 30 cases there was some such atherosclerosis but in many of these only a few arteries were affected. In every case in which atherosclerosis was severe enough to affect the lumen of a pulmonary artery it occurred in a lower zone artery. Most of such narrowing was focal and almost invariably the narrowing seen in the lower zones in angiograms was due to the muscular contraction of hypertrophied arteries and was only very rarely due to irreversible atherosclerosis.

The pulmonary veins showed hypertrophy analogous to that seen in the arteries and in them too hypertrophy was greater in the lower zones (Fig. 11B).

(*b*) *Congenital Group.* In spite of their dilatation, the proximal arteries showed hypertrophy. The distal arteries, where they were of similar diameter to the controls, also showed hypertrophy. The degree of medial hypertrophy was of the order of 2 to 3 times both centrally and peripherally and in contrast to the mitral cases there was no detectable difference in the degree of hypertrophy in the upper and lower zones (Fig. 11C). Atherosclerosis was minimal in all cases but the number examined was too small for this finding to be of much significance. Changes of the type described by Brewer (1955) were noted but these affected only the smallest arteries and are not germane to the present problem.

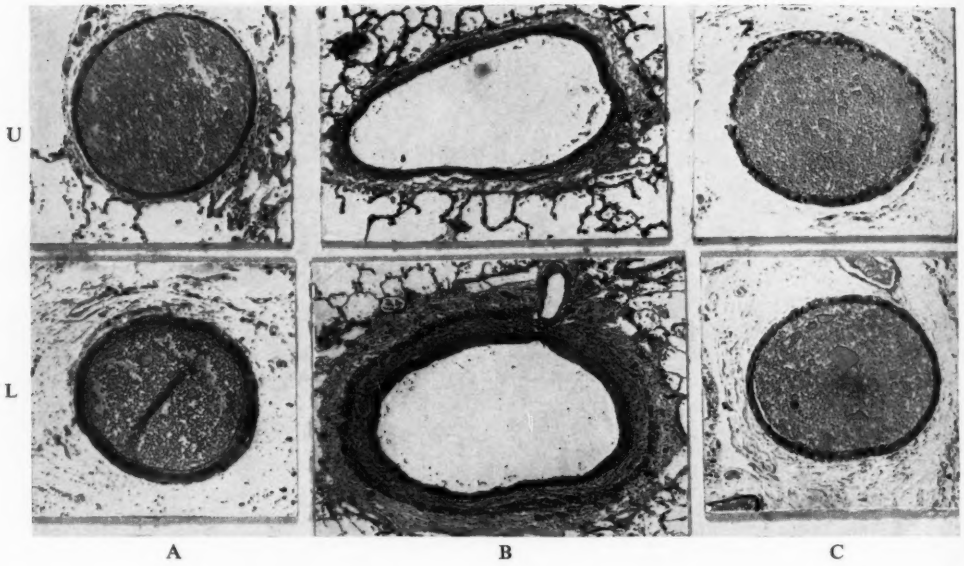


FIG. 11.—(A) Small pulmonary arteries from the lower (L) and upper (U) lobes in a patient with mitral stenosis (the same case as Fig. 8). The vessels are of comparable size (2 cm. from pleura), and of equal magnification. Injection mass fills the lumen of each vessel. The thickness of the media in the lower lobe vessel is 2 to 3 times that of the upper. ×45. (B) Pulmonary veins from the lower (L) and upper (U) lobes in a patient with mitral stenosis (same case as Fig. 8). The vessels are of comparable size (2 cm. from pleura), and equal magnification. The thickness of the media of the lower lobe vein is 4 times that of the upper. ×24. (C) Small pulmonary arteries from the lower (L) and upper (U) lobes in a case of atrial septal defect with severe pulmonary hypertension. The vessels are of comparable size (2 cm. from pleura), and equal magnification. Injection mass fills the lumen. The thickness of the media is equal in both vessels and is 2 to 3 times that of normal. ×45.

DISCUSSION AND CONCLUSIONS

These studies show that there are differences in the pulmonary vascular patterns and behaviour between mitral stenosis and congenital heart disease with shunts. These differences are most striking (especially in mitral stenosis) when severe pulmonary hypertension is present.

In mitral stenosis, as we have previously shown (Davies *et al.*, 1953), the degree of narrowing of the peripheral arteries and of enlargement of the main arteries is proportional to the severity of the pulmonary hypertension present. The narrowing of the small branches was confined to the lower and mid zones of the lungs and did not affect the apical regions; the narrowing involved arteries as proximal as branches of the segmental arteries. These changes can be seen in angiocardiograms in life, and in many cases in plain X-rays. They were confirmed by post-mortem arteriography and histological studies (Fig. 1, 2, 8, and 11).

In congenital heart disease there was considerable enlargement, dilatation, and tortuosity of the main and major branches of the pulmonary artery when a left-to-right shunt was present. This enlargement often extended into the small branches, which were also tortuous. Post-mortem arteriography has shown that when severe pulmonary hypertension has been present in life, there is narrowing of the very small branches which shows as lack of " background " filling, and that even small branches may be dilated and tortuous. This loss of " background " filling is uniform throughout the lung and there is no localization to the lower zones, in sharp contrast to mitral stenosis (Fig. 9). Histological studies confirm these differences in distribution (Fig. 11c).

Radiological studies in life, however, do not give a clear indication of the presence or absence of severe pulmonary hypertension in the congenital group, again in contrast to mitral stenosis, and while oligæmia of the peripheral lung fields may be seen in severe hypertensive cases with bi-directional shunts (Fig. 3 and 5), there are many exceptions (Fig. 4 and 6). It is probably safe to say, however, that its presence usually indicates severe hypertension and actual or impending reversal of the left-to-right shunt.

Since the narrowing of the pulmonary arteries involves the smallest branches it is not surprising that it is not detectable in plain X-rays or even on angiography (Fig. 6).

It is probable that high pulmonary arterial pressures in this group can result from increases in flow, which dilate even the small arteries. In cases with a large left-to-right shunt and torrential pulmonary blood flow this dilatation then extends into branches at the periphery of the lungs, giving a picture of overfilled vessels in the presence of a high pulmonary pressure. When the resistance rises in the very small vessels, the left-to-right shunt tends to be reduced, and thus the dilatation of the peripheral vessels becomes less. Therefore the state of the peripheral pulmonary arteries, and the degree of filling seen radiologically will depend upon the balance between the magnitude of the left-to-right shunt and the resistance offered by the smallest arteries and arterioles.

In mitral stenosis the situation is less complex, since the pulmonary blood flow is not increased and the small branches of the pulmonary artery are not dilated as a result. Dilatation of the main pulmonary arteries is the result of pulmonary hypertension alone. Furthermore, the localization of the arterial narrowing to the lower zones, and its presence in branches of a size easily detectable radiologically, permits a reliable correlation between pressure and radiological appearances.

A further contrast between the two groups, which is of great interest although not necessarily directly related to the differences in vascular patterns, lies in the response to hypotensive drugs. The ready fall in pulmonary vascular resistance obtained in mitral stenosis did not occur in the congenital group. The latter group, however, are extremely difficult to study in this way; the results of further work will be reported elsewhere.

The Genesis of the Different Vascular Patterns in Mitral Stenosis and Congenital Heart Disease. We believe that the clue to the difference between the two groups lies in the pulmonary venous pressure. This is not uniform throughout the lungs because of hydrostatic differences between different areas. In the erect posture it will be higher at the bases than the apices.

In mitral stenosis, the left atrial pressure is significantly increased by the obstruction of the mitral valve. This results in pulmonary venous hypertension which will be augmented at the bases by the hydrostatic increment, and this may reach a critical level for oedema formation. We believe that this critical venous pressure results in arterial constriction in the lower, and later in the mid zones. Because of the negative hydrostatic pressure at the apices relative to the left atrium, very high left atrial pressures, well above the critical level for œdema formation, would be required for arterial constriction to occur at the apices; we have never seen this. The finding of greater muscular hypertrophy in lower lobe pulmonary veins than in upper lobe veins strongly supports this explanation (Fig. 11B).

It has been suggested that in mitral stenosis the pulmonary arterial pressure rises passively in proportion to the left atrial pressure, until the latter reaches a critical level for œdema formation, after which small increments of left atrial pressure cause large increases in pulmonary arterial pressure indicating active arteriolar constriction (Dexter *et al.*, 1950; Holling, 1952; Blacket *et al.*, 1953).

We believe, however, that active arterial constriction at the bases of the lung may develop at lower levels of left atrial pressure. In a previous report (Davies *et al.*, 1954) it was shown that in patients with severe pulmonary hypertension the injection of small amounts of hexamethonium into the pulmonary artery is followed by a larger fall in pulmonary, than in systemic, arterial pressure, without a fall in cardiac output. Our more recent observations have shown a similar selective fall in pulmonary vascular resistance in patients with only modest pulmonary hypertension. These results will be reported elsewhere.

The radiological appearances of diffuse haziness in the lower zones probably represents chronic transudation from the capillaries which is the result of the locally increased basal venous pressure. By contrast " acute massive " pulmonary œdema is diverted to the central core of the lung, and sometimes to the apices, by the arterial vasoconstriction at the bases which prevents extensive rapid transudation there. Fig. 10 shows pulmonary œdema confined to the mid and apico-posterior zones in a patient who had severe mitral stenosis with pulmonary hypertension in life. The localization of the transverse costophrenic lines to the bases harmonizes with this concept and suggests that they are due to interlobular œdema, as suggested by Fleischner and Reiner (1954), although impaired lymphatic drainage (Shanks and Kerley, 1951), lymphatic dilatation (Levin, 1955), or over production of lymph may be a factor.

Our findings shed some light on the concept of a " protective " increase in arteriolar resistance which has been said to prevent pulmonary œdema (Lewis *et al.*, 1952; Logan and Turner, 1953; Wood, 1954). We have previously challenged this concept (Davies *et al.*, 1954) believing that patients with severe pulmonary hypertension and arterial disease are as likely, or more likely, to have attacks of œdema as those with modest pulmonary arterial hypertension and considerable pulmonary venous hypertension. The results of the present investigation indicate that the arterial changes prevent massive pulmonary œdema only at the bases, and divert it to other portions of the lung (upper and central zones). It would thus be reasonable to speak of " redistributive ", or perhaps " locally protective " arterial narrowing.

In congenital heart disease with pulmonary hypertension and a shunt, the pulmonary venous pressure is usually normal (Swan *et al.*, 1954; Bruwer *et al.*, 1955; Rossall and Gunning, 1956). Therefore, the hydrostatic increment that exists at the bases will not increase the venous pressure there to a critical degree. A critically raised pulmonary venous pressure can, therefore, be excluded as a cause of the arterial changes in the congenital group, so that in contrast to mitral stenosis, the arterial changes are generalized throughout the lungs.

It has previously been suggested that narrowing of the pulmonary arterioles is, at least in part, due to the torrential pulmonary flow (Hultgren *et al.*, 1953; Civin and Edwards, 1950), and our findings of narrowing in the small arteries in all zones of the lungs are consistent with this hypothesis, although we can offer no proof.

However, other factors may be implicated, such as abnormalities of the vessels themselves (Civin and Edwards, 1951; Welch and Kinney, 1948; Evans, 1951).

The extreme rarity of acute or chronic pulmonary œdema in congenital heart disease with shunts is likely to be due to the low levels of left atrial pressure. However, horizontal costophrenic lines are sometimes seen, although not as frequently or extensively as in mitral stenosis (Bruwer *et al.*, 1955; Rossall and Gunning, 1956). They were present in 4 of our congenital cases (3 with severe pulmonary hypertension). We believe that they are then the result of either increased left atrial pressure due to torrential left atrial flow, or left ventricular failure, or perhaps to abnormalities of lymph flow induced by the large pulmonary blood flow.

Summary

A combined radiological, hæmodynamic, and pathological study of the pulmonary vascular system has been made in two groups of cases—mitral stenosis and congenital heart disease with pulmonary hypertension and shunts.

Striking differences in the pulmonary vascular pattern were found between the two groups.

In mitral stenosis, arterial narrowing was confined to the lower and mid zones, and involved the branches of segmental arteries, but was not present in the upper zones.

In the congenital group all the branches were dilated and tortuous, except the very fine arteries which were reduced in size. There was no regional localization; the changes being diffuse throughout the upper, mid, and lower zones.

There were also differences between the two groups in the response of the pulmonary vasculature to hypotensive drugs. The reasons for the differences are discussed.

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ADDITIONAL ELECTROCARDIOGRAPHIC SIGNS OF CARDIAC PAIN

BY

WILLIAM EVANS AND R. K. PILLAY

From the Cardiac Department of the London Hospital

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The recognition of the lesser changes in the electrocardiogram that indicate a limited injury of the myocardium from coronary arterial disease has reduced significantly the number of patients with cardiac pain erstwhile regarded as showing a normal tracing. Such changes include depression of any part of the S–T segment, low or blunt T waves, terminal dipping of the T wave, inversion of the U wave, notching of the descending limb of the QRS in lead CR7, and the appearance of a Q wave in IIIR when it has been absent in lead III (Evans and McRae, 1952; Evans, 1951). Although such deformities in the cardiogram are small ones, they loom large in their significance, because in the first place they confirm a cardiac source for pain in the chest, and secondly because the mortality rate among patients showing them is the same as in those with gross changes like deeply inverted T waves with or without abnormal Q waves.

The purpose of this inquiry has been to find other cardiographic changes which might signify that chest pain in a given patient arises from coronary arterial disease. We have sought the meaning of two other lesser deformities; the first has been a depression of the T–U segment, and the second the presence of a natural Q wave in certain leads.

Outline of the Investigation

Before either of the two cardiographic changes could be accepted as representing a myocardial fault, it was required of them to satisfy certain probationary tests. First, the deformity should be absent from the electrocardiogram of healthy youths, although it might occasionally appear in the tracings recorded in uncomplaining elderly subjects when it could indicate a painless cardiac injury. Secondly, the deformity was expected in tracings from patients with chest pain that seemed characteristic of cardiac pain, either as a lone sign or in company with other signs accepted as evidence of coronary arterial disease. Thirdly, the empirical deformity residing in a tracing recorded at rest should be frequently joined in the exercise electrocardiogram by more obvious changes accepted as meaning a positive test. Fourthly, the cardiographic deformity might in time give way to unequivocal changes of cardiac infarction, or the patient exhibiting the sign might die from extension of the infarct.

The electrocardiogram in each instance consisted of the four bipolar limb leads I, II, III and IIIR (lead III recorded during deep inspiration), together with the three bipolar chest leads CR1, CR4 and CR7. The bipolar leads were deliberately chosen as being more proficient than unipolar leads in the investigation of cardiac pain.

We first examined the tracing in two separate series each comprising 500 healthy adults over the age of 20 years, who showed neither clinical nor radiological signs of cardiovascular disease. It was next examined in 200 consecutive patients in whom the chest pain resembled cardiac pain, but the tracing had been reported as normal on casual inspection, and in another 500 patients with cardiac pain confirmed by characteristic electrocardiographic changes. Lastly, the cardiogram was examined in 250 patients with painless heart disease. It was in these 1950 cases that we sought

the two newer electrocardiographic changes that we submitted to special scrutiny in order to test their dependability as evidence of a limited myocardial injury. The results of the inquiry in regard to each cardiographic deformity are now to be discussed separately.

Depression of the T–U Segment

The significance of a sharp dip of the descending limb of the T wave beyond the iso-electric level has already received emphasis (Evans and McRae, 1952; Evans, 1955), for it proved to be as useful as frank inversion of the T wave in the recognition of a myocardial injury from coronary arterial disease.

On this occasion the significance of a less abrupt and more gradual depression in the T–U segment has been examined. This trough-like deformity involved the entire length of the T–U period, and although shallow, it extended below the iso-electric line, here determined by reference to the U–P interval. In the presence of tachycardia, therefore, it is not possible to recognize this deformity in that the early incidence of the P wave in this circumstance does not allow the curve to return to its iso-electric phase for the U–P interval is eliminated (Fig. 1).

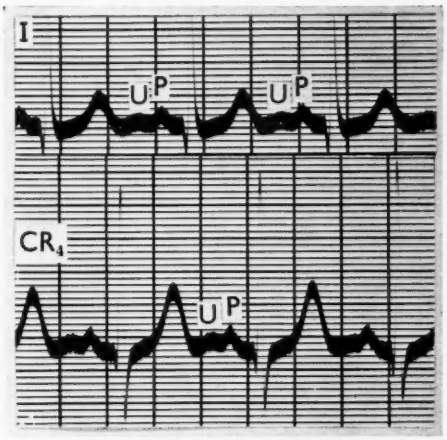

Fig. 1.—Apparent depression of the T–U segment. Tachycardia has annulled the U–P interval so that the P wave is superimposed on the final phase of the U wave.

In our cases the downward projection of the T–U depression beyond the U–P line was never greater than 1·0 mm., and in order to be discernible, and consequently significant, it had to be 0·25 mm. (Fig. 2).

When this deformity was sought in 500 consecutive electrocardiograms recorded from healthy adults it was never found. Later, it was looked for in tracings from 250 patients with diverse

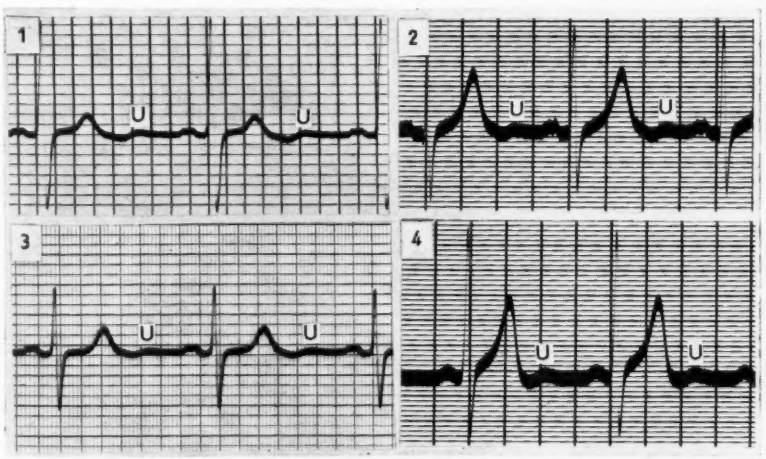

Fig. 2.—Depression of the T–U segment in lead CR4 in four patients with cardiac pain. The horizontal lines indicating voltage, mark out intervals of 2 mm. in Cases 1 and 3 and 1 mm. in Cases 2 and 4.

forms of painless heart disease where coronary arterial disease was not suspected; it was met with once in a child with the Fallot syndrome.

Depression of the T–U segment was next sought in 500 patients, considered to have cardiac pain, but in whom gross electrocardiographic changes were absent; it was found 15 times.

The sign was best seen in lead CR4 in 12 of the cases, and in CR7 in the other 3; in eight it appeared in lead I as well. In eight it was associated with other lesser electrocardiographic signs, namely depression of the S–T segment in IIIR in five, notching of the RS limb in CR7 in two, addition of a Q in IIIR in one, and inversion of the U wave in another. In seven patients depression of the T–U segment was there by itself as the only discernible deformity in an otherwise normal tracing. The exercise electrocardiogram, recorded in five, gave a positive test in four (Fig. 3). Two of the patients have since died suddenly from extension of cardiac infarction, which was confirmed at necropsy in both instances when the infarct was found at the back of the left ventricle.

Natural Q Waves in Limb and Chest Leads

By definition any downward deflection preceding the R wave is a Q wave. In adults a Q has usually been regarded as natural if its width does not exceed 0·04 second, and if its depth does not

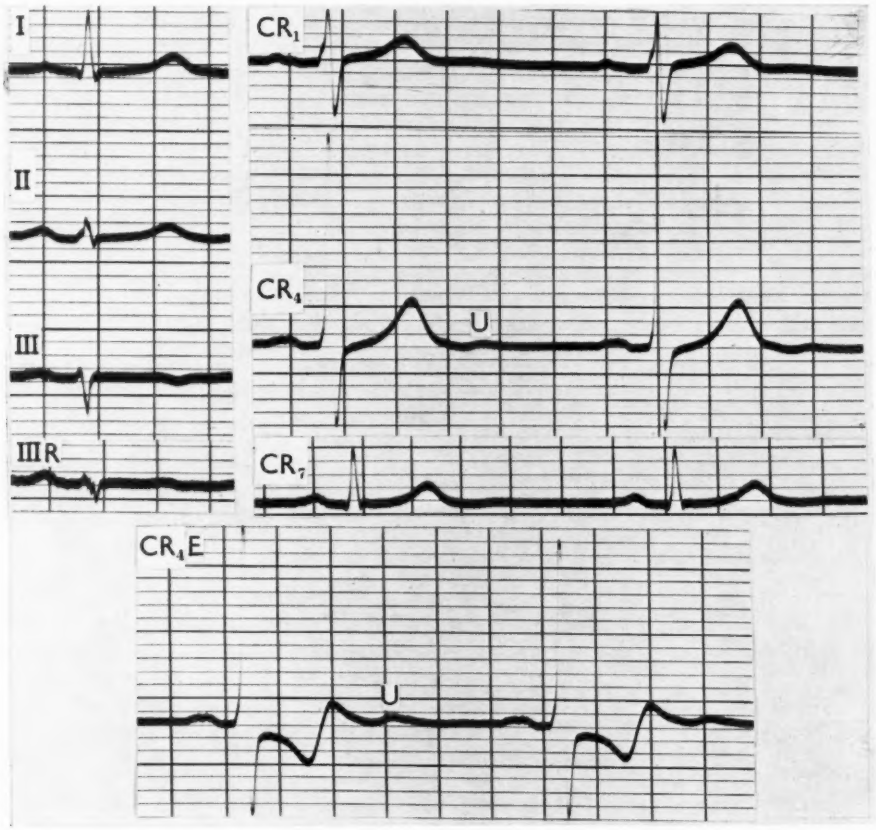

Fig. 3.—Depression of the T–U segment in CR4 was the only cardiographic abnormality in a patient with cardiac pain. The exercise tracing (CR4E) was a positive test where the T–U interval is natural.

exceed 4 mm. in the limb leads I, II, and IIIR; it may be deeper in lead III, especially in children.

Speaking on the initial ventricular deflection in the electrocardiogram of the young healthy subject, Kossman *et al.* (1936) said that the maximal measurement of Q in each of leads I, II, and III in 178 cases was 2 mm., 2·5 mm. and 3·0 mm. respectively. Wilson (1937) found that the depth of the Q wave in leads I, II and III, was less than 2·5 mm., 3·3 mm. and 3·5 mm. respectively in 104 healthy subjects between the ages of 20 and 30 years. Lepeschkin (1951), seeking the same measurement in 4000 healthy adults collected from various sources, found the corresponding values to be 3 mm., 4 mm., and 4·5 mm. Graybiel (1951) mentioned that a Q of less than 3 mm. in depth may be seen in lead I in half the tracings from healthy subjects, and in leads II and III in two-thirds of them.

Several workers have given their views on the maximum depth of the Q wave in chest leads. Deeds and Barnes (1940) found this to be 1·7 mm. deep in CR5 and 2·6 mm. in CR6 in 100 healthy adults; a Q was only once present in CR1. Levine (1948) mentioned that a Q wave was not normally seen in the chest leads V1 to V3, and was not prominent until V5 or V6 was reached; such a Q was thin, rarely longer than 0·02 second, and was never more than a small fraction of the R wave. Lepeschkin (1951) in a series of healthy subjects over the age of 20, reported that the maximal depth of the Q was 0·5 mm. in V3, 1·6 mm. in V4, 3·0 mm. in V5 and 2·7 mm. in V6; it was absent from leads V1 and V2. Graybiel (1951) also mentioned that in healthy subjects a Q was never seen in chest leads V1 and V2; it was rare to see a small Q in V3, but it was seen sometimes in V4, commonly in V5, and frequently in V6. White (1951) similarly stated that Q waves might be absent from chest leads in health, but that small ones appeared in leads over the left ventricle.

It will be seen, therefore, that these several observers are agreed that natural Q waves are expected in leads taken over the left chest, but are not found in health in leads recorded over the right ventricle. Our findings are in accord with these views, but we have been unable to find any observations made on the normality or otherwise of natural Q waves appearing in a combination of limb and chest leads, and it is with this problem that we are concerned.

Lead Distribution of Natural Q Waves. In addition to a search for natural Q waves in each of the seven leads used in this investigation, we also sought them in 33 different lead combinations. When this was done in 500 symptomless and apparently healthy adults, a Q was absent in 19 and present in 14 combinations. The significance of this finding is now to be examined for each group.

Absence of natural Q waves in the healthy series. The particular leads that did not show a Q wave in the healthy series are listed in Table I. Thus, a Q was absent in four individual leads, in four two-lead combinations, in four three-lead combinations, in five four-lead combinations, and in two five-lead combinations.

The absence of Q waves in these lead arrangements might mean that the distribution of electrical

TABLE I

SINGLE LEADS OR COMBINATION OF LEADS THAT DID NOT SHOW A Q WAVE IN 500 SYMPTOMLESS AND APPARENTLY HEALTHY SUBJECTS

Number of leads in combination	Leads specified
Single lead	I. II. IIIR. CR4.
Two leads	I and II. I and CR4. II and CR4. CR4 and CR7.
Three leads	I, III, and IIIR. I, II, and CR4. II, CR4, and CR7. III, IIIR, and CR4.
Four leads	I, II, III, and IIIR. I, III, IIIR, and CR4. I, III, IIIR, and CR7. II, III, IIIR, and CR4. III, IIIR, CR4, and CR7.
Five leads	I, II, III, IIIR, and CR4. I, III, IIIR, CR4, and CR7.

potential associated with heart contraction is such as not to allow them to appear, and that their presence would suggest that the spread of the electrical forces was being modified by a myocardial injury. It was necessary, therefore, to look for Q waves in the same lead arrangement recorded in patients with chest pain that seemed characteristic of cardiac pain.

A natural Q, which was never an isolated finding in lead I among the 500 healthy subjects, was met with once in the series of patients with chest pain (Fig. 4).

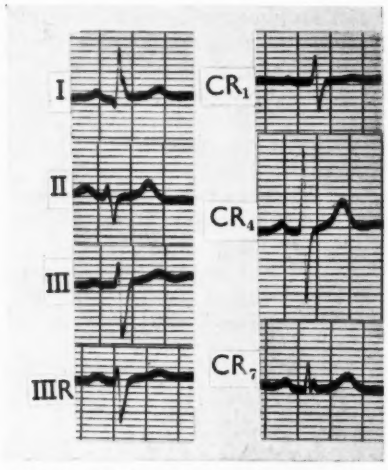

FIG. 4.—A Q wave in lead I was the only deformity in the electrocardiogram of a patient with cardiac-like pain. The notch in RS7 is not considered abnormal in that it is placed low on the stem and a qR pattern is absent.

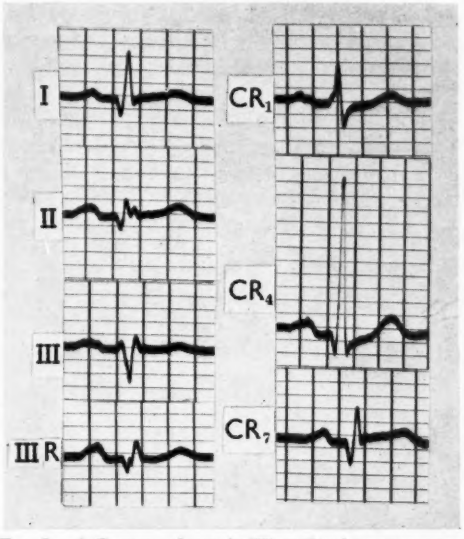

FIG. 5.—A Q wave, absent in III, makes its appearance in IIIR. The tracing was from a patient with proved cardiac pain.

This investigation confirmed the view that the appearance of a Q wave in IIIR that had been absent in III was evidence of cardiac infarction in a patient with chest pain. This occurred three times as a lone cardiographic abnormality in our series (Fig. 5), and since its implication has been discussed fully elsewhere (Evans, 1951), it will not be described further in this paper.

In the two other single leads, namely II and CR4, no patient with chest pain in the series showed a Q wave in these leads, nor did any in the group of healthy subjects.

We have been reluctant to pronounce on the significance of a Q wave in the other lead combinations named in Table I, because although they never showed a Q in the series of healthy subjects, neither did they in patients with cardiac pain whose electrocardiograms subsequently gave unequivocal evidence of cardiac infarction.

Presence of natural Q waves in the healthy series. It might be held, and with justification, that a Q that appeared frequently in certain lead combinations among uncomplaining and apparently healthy subjects could not be regarded as evidence of a myocardial injury should it appear in patients with chest pain. In the case of the lead arrangement I-CR4-CR7, however, we were impressed by the relative absence of a Q wave in the younger group and its frequency in the older group. Thus, among 42 cases exhibiting this cardiographic sign, there were only 6 under 50, while 22 were over 60 years of age (see Table II). In order to test the meaning of this finding and to discover whether this told of the effects of coronary arterial disease, the 42 supposedly healthy subjects presenting this sign were recalled for examination. Twenty failed to attend and in most of these it was ascertained that they felt it was unnecessary to present themselves for further examination in that

they relied on the reassurance given them at the first. One case, however, had died at home from pneumonia.

Among the 22 who responded we considered that one was too old and frail to be subjected to an exercise electrocardiogram. Such a test was carried out in 15 when nine gave a positive result, four a doubtful positive, while in two it was regarded as negative. At this stage the significance of such a result came under review, especially as to the meaning of a negative response because in our two cases a Q in the combination I-CR4-CR7 was associated with other abnormal signs (Fig. 6). While we have regarded the positive test as likely to be significant we would hesitate to accept a negative one as opposing a doubtful change in the resting cardiogram as meaning a myocardial fault, unless this applied to a number of the cases.

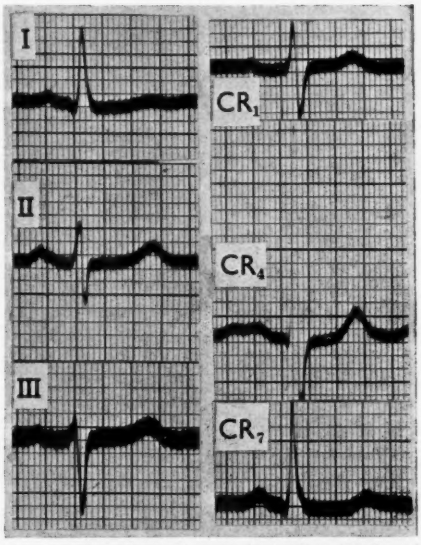

FIG. 6.—A natural Q wave in leads I, CR4, and CR7 from a patient with cardiac pain is accompanied by S–T depression in I and CR7. An exercise test failed to exaggerate this deformity.

In the remaining 6 of the 22 cases that attended for re-examination a Q wave was no longer present in the I-CR4-CR7 combination, and this led us to consider a definition of a significant natural Q wave, for inspection of the first electrocardiogram taken in these six cases showed that it was a diminutive wave, appearing as a mere point, and less than 1 mm. in depth (Fig. 7). We would, therefore, define a significant natural Q in adults as being over 1 mm., but not exceeding 3 mm. in depth, except in lead III, and not exceeding 0·04 second in width.

We next sought a Q wave in the lead combination I-CR4-CR7 in the series of patients with chest pain that seemed to be characteristic of cardiac pain. There were six such cases. When their progress was followed it was found that more obvious electrocardiographic changes had taken place in association with recurrent attacks of chest pain in four (Fig 8 and 9). One other had died from extension of cardiac infarction (Fig. 10). The remaining patient continues

TABLE II

AGE INCIDENCE AND LEAD DISTRIBUTION OF NATURAL Q WAVES AMONG 500 HEALTHY ADULTS

	Age groups in decades	20 to 29 years	30 to 39 years	40 to 49 years	50 to 59 years	60 to 69 years	70 years or over
	Number of cases	50	86	129	143	79	13
Leads or combination of leads	Absent in all leads (48)	8	5	10	15	9	1
	CR7 (38)	2	6	14	13	3	0
	I and CR7 (99)	4	20	28	34	13	0
	I, CR4, and CR7 (42)	0	2	4	14	16	6
	I, II, and CR7 (48)	4	10	13	13	7	1
	I, II, CR4, and CR7 (44)	5	3	13	11	10	2
	I, II, III, IIIR, CR4, and CR7 (35)	4	6	7	10	8	0
	I, II, III, IIIR, and CR7 (37)	5	6	10	14	2	0
	II and CR7 (13)	0	3	5	2	3	0
	II, III, and IIIR (5)	0	1	1	2	1	0
	II, III, IIIR, and CR7 (71)	13	22	15	12	6	3
	II, III, IIIR, CR4, and CR7 (11)	1	0	7	2	1	0
	III and IIIR (5)	2	2	0	1	0	0
	III, IIIR, and CR7 (4)	2	0	2	0	0	0

Numerals in and outside the brackets denote number of cases.

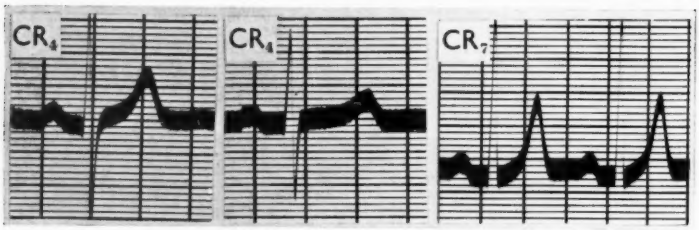

FIG. 7.—A diminutive, and therefore insignificant, Q wave in tracings taken from three healthy subjects. The Q is seen as a mere point.

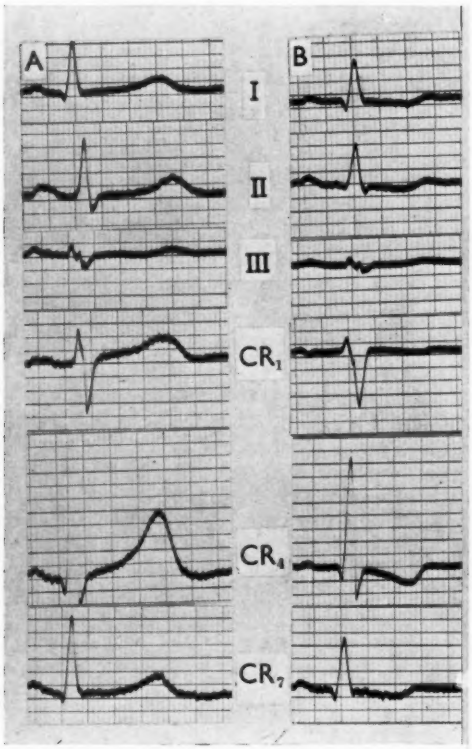

FIG. 8.—A natural Q in leads I, CR4, and CR7 was the only abnormal sign in the cardiogram (A) taken from a patient with cardiac pain. Another time the tracing (B) showed more obvious changes from extension of the cardiac infarct.

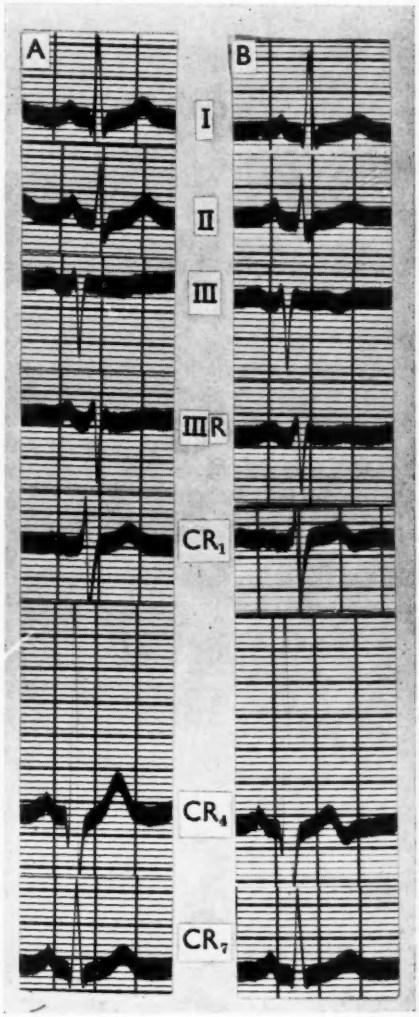

FIG. 9.—A natural Q in leads I, CR4, and CR7 was the only abnormal sign in the cardiogram (A) from a patient with cardiac pain. More obvious changes of cardiac infarction are seen in (B) recorded two weeks later.

to experience typical attacks of cardiac pain although his cardiogram remains unchanged. These findings are at variance with the suggestions made by Burch (1956) that patients showing an absence of Q in leads I, V5 and V6 are prone to cardiac pain and septal fibrosis in the absence of coronary occlusion. Indeed, apart from finding a Q in the lead combination I-CR4-CR7 in six patients with cardiac pain, we found it absent in 58 of the 500 healthy subjects.

In that a Q in this lead combination may prove to be significant, the combination I-CR4 could prove to be equally so should a displacement of the heart cause the CR7 lead to occupy a position in relation to the heart farther to the right than its customary one opposite the postero-lateral border of the left ventricle. No such example was, however, met with in the course of this investigation.

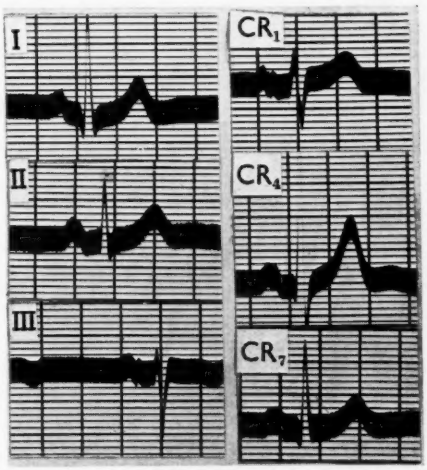

FIG. 10.—A natural Q wave in leads I, CR4, and CR7 was the only abnormal sign in a patient with cardiac pain who died three months later from further cardiac infarction.

SUMMARY AND CONCLUSIONS

The competence of two further lesser electrocardiographic signs in the diagnosis of a limited myocardial injury from coronary arterial disease has been examined.

The two probationary signs were a depression of the T–U segment, and the presence in certain lead combinations of a natural Q wave, defined as one not less than 1 mm. and not more than 3 mm. in depth, and no wider than 0·04 second.

To prove the validity of each cardiographic sign as a teller of cardiac pain we required that it should be absent in healthy youths and infrequent in uncomplaining elderly subjects; when present in such symptomless subject or in patients with chest pain, the sign was expected either to give way later to more obvious ones indicating cardiac infarction, or to be joined with changes in the exercise electrocardiogram that meant a positive test. The demise of a patient from cardiac infarction without offering intermediate electrocardiographic evidence was also accepted as corroboration of the reliability of the probationary sign.

Depression of the T–U segment below the isoelectric line of the U–P period proved to be an undisputed sign of a myocardial injury from coronary arterial disease. It is not possible to discover this change in the presence of tachycardia because the early incidence of the P wave prevents the return of the curve to an iso-electric phase during the U–P period.

The incidence of natural Q waves in cardiograms from healthy subjects and from patients with cardiac pain led us to draw the following conclusions. First, a natural Q in the single leads or in lead combinations, listed in Table I is evidence of a myocardial injury. Secondly, although a Q in the lead combination I-CR4-CR7 was seen in healthy subjects, since it usually appeared in the older age group, and since it was found as the only unnatural sign in the cardiogram recorded from patients in whom chest pain was later confirmed to be cardiac pain when extension of the cardiac infarct had taken place, we believe that Q in this lead combination may also prove to be an early electrocardiographic sign of a myocardial injury.

We wish to acknowledge the help we obtained from Dr. J. W. Fawcett earlier in the investigation.

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THE EFFECT OF SERPASIL IN PULMONARY HYPERTENSION

BY

D. HALMAGYI,* B. FELKAI, Z. CZIPOTT, AND G. KOVÁCS

From the Medical and Surgical Cardiovascular Division, of the First Department of Medicine, University Medical School, Szeged, Hungary

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A considerable amount of information has been accumulated concerning the effect of various hypotensive agents on the pulmonary circulation. A detailed account on these observations was given recently by one of us (Halmagyi, 1957). Most of these studies were carried out in patients suffering from mitral stenosis. It was concluded that the increase of pulmonary vascular resistance in this disease is due both to organic changes and to vasoconstriction, the latter being mediated by the nervous system (Halmagyi *et al.*, 1953). No uniform action was, however, obtained by drugs acting on different parts of the nervous system: even similar-acting drugs had a different effect on the pulmonary circulation. Tetra-ethylammonium (Halmagyi *et al.*, 1953; Scott *et al.*, 1955), dibenamine, sodium nitrite, and sleep (Halmagyi *et al.*, 1953) resulted in a decrease in pulmonary arterial pressure and resistance. On the other hand, hexamethonium failed to influence pulmonary vascular resistance in carefully controlled observations carried out in patients suffering from mitral stenosis (Storstein and Tveten, 1954).

There were many disadvantages in the therapeutic use of the substances mentioned above. The necessity of a parenteral rout of administration, their rapid excretion and, last but not least, their strong hypotensive action on the systemic circulation discouraged their widespread use. Schumann (1954, 1955) has recently pointed out that long-term peroral administration of serpasil to patients suffering from mitral stenosis resulted in an apparent amelioration of their complaints. This effect was attributed by him to general sedation and bradycardia, brought about by this medicament. It was therefore decided to investigate the effect of serpasil on the lesser circulation.

Material and Methods

Fifteen patients, aged 17 to 45 years, were investigated. All were submitted for assessment of the need for surgical treatment of their heart disease. None was in manifest heart failure at the time of observation. All the patients shown in Table I suffered from mitral stenosis with the exception of Case 2 (isolated pulmonary stenosis of slight degree), Case 4 (patent ductus arteriosus), and Case 13 (ventricular septal defect with pulmonary hypertension).

Cardiac catheterization was performed in the usual manner as described before (Halmagyi *et al.*, 1952 and 1953). No sedation was given: apprehensive patients were considered unsuitable for this kind of observation. The tip of the catheter was placed in the pulmonary artery and an arterial cannula was placed in the femoral or brachial artery. Both procedures were done under local anæsthesia. A sufficient time was allowed then for stabilization.

Pulmonary " capillary " pressures were obtained. Blood was withdrawn in all cases from the catheter tip in this position. The catheter was then withdrawn to the main pulmonary artery under

* Present address: Miners' Chest Disease Treatment Centre, Llandough Hospital, Cardiff.

TABLE I

THE EFFECT OF SERPASIL ON THE LESSER CIRCULATION IN PULMONARY HYPERTENSION OF VARIOUS ORIGIN

No.	Ref. No.	Cardiac index, litres		Pulmonary arterial pressure		Pulmonary "capillary" pressure		Femoral arterial pressure		Pulmonary arteriolar resistance		Total pulmonary resistance		Peripheral arterial resistance	
		B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	284	3·60	4·20	11	9	7	6	87	90	89	57	244	171	1935	1757
2	213	3·55	2·58	14	11	9	6	100	90	112	155	316	341	2260	2760
3	306	3·20	3·20	16	14	11	12	100	90	126	50	400	350	2500	2250
4	348	5·88*	–	21	21	16	16	87	87	68	–	286	–	2000	–
5	292	4·25	5·00	22	17	14	11	105	105	150	96	414	272	1978	1678
6	309	3·86	3·17	22	16	19	15	100	100	62	25	456	404	2070	2520
7	330	4·09	3·23	24	20	16	9	90	82	157	272	472	496	1762	2035
8	282	–	–	25	25	22	15	120	120	–	–	–	–	–	–
9	298	1·83	2·61	27	31	21	24	90	90	262	214	1180	950	3940	2760
10	349	6·34	6·08	32	21	24	17	105	102	101	39	406	263	1330	1350
11	324	2·53	2·20	39	29	31	30	82	79	224	34	1230	1055	2580	2870
12	317	2·81	2·81	40	40	34	34	105	98	170	170	1285	1285	3100	2790
13	335	5·43*	6·93*	58	33	3	3	90	100	810	348	870	381	2300	2660
14	350	2·89	2·98	66	31	–	–	110	110	–	–	1828	808	3050	2870
15	333	3·51	3·51	72	59	36	36	100	95	822	525	1640	1340	2280	2160

All pressures represent mean pressures, expressed in mm. Hg. Resistances are given in dyne sec. cm.$^{-5}$m.^{2} B.S.A. Flow values signed with * represent pulmonary flow.

B=before, A=30 min. after serpasil.

fluoroscopic guidance. Pulmonary and femoral arterial pressures were then measured. All pressures were taken with Sanborn electromanometers and recorded on a multichannel oscillograph. Cardiac outputs were determined by the direct Fick method. Oxygen consumption was measured by using a Noyons-type of diapherometer (Kipp, Delft). During this procedure, simultaneous blood samples were obtained from the pulmonary artery and the femoral or brachial artery. The blood samples were analysed for oxygen by a whole-blood oximeter of the hæmoreflector-type (Kipp, Delft). Hæmoglobin content was determined photoelectrically.

The above procedures were followed by injecting 1 mg. of serpasil into the catheter in a period of four minutes. Pulmonary arterial, pulmonary "capillary", and femoral arterial pressures and cardiac output were measured in every tenth minute repeatedly. In measuring pulmonary capillary pressure the catheter was wedged apparently in the same site on each occasion. Forty minutes following the injection of the drug, the observation was terminated.

Mean pressures were obtained by electric integration. The zero point for all measurements was 10 cm. anterior to the back, with the patient recumbent. Pulmonary arteriolar resistance, total pulmonary resistance, and systemic resistance were calculated according to the well known formulae.

Results

Our detailed results are shown in Table I; only some main features are emphasized below. Since a significant change in heart rate never occurred, its values were omitted from the table which contains the individual cases arranged in the order of the level of pulmonary arterial pressure.

In *mitral stenosis*, administration of serpasil was followed by a decrease of pulmonary arterial pressure and resistance. In most cases pulmonary "capillary" pressure remained unchanged. No change occurred in systemic arterial pressure and resistance, and cardiac output remained generally identical. The mean changes are illustrated in Fig. 1. Mean diminution of pulmonary arterial pressure and resistance amounted to 30 per cent, and that of total pulmonary resistance to 23 per cent. Pulmonary resistance increased in Case 7, and remained unchanged in Case 12. In the former the simultaneous presence of tricuspid stenosis was established, while the latter patient died three weeks after mitral valvotomy as a consequence of recurrent pulmonary embolism and an obstructing thrombosis of the left atrium.

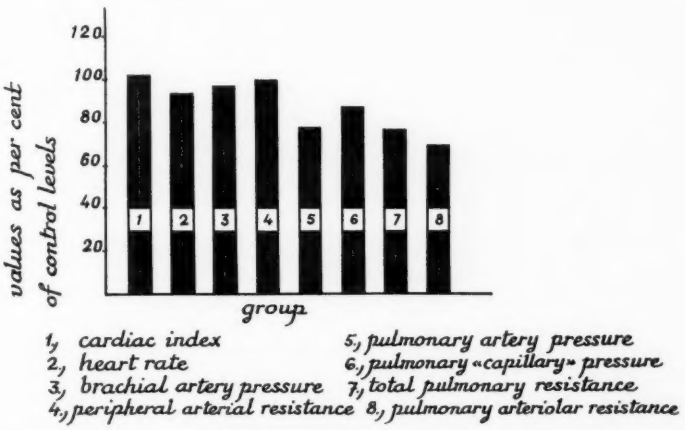

FIG. 1.—Mean change of hæmodynamic data in 12 patients suffering from mitral stenosis following the administration of serpasil. Control values are indicated as 100 per cent.

Serpasil failed to influence pulmonary arterial pressure and resistance in *pulmonary stenosis* (Case 2) and in *patent ductus arteriosus* (Case 4).

A 50 per cent reduction in pulmonary arterial pressure and resistance followed the administration of serpasil in a patient suffering from *ventricular septal defect* complicated by pulmonary hypertension (Case 13). At the same time systemic pressure and resistance increased. Thus the increase of pulmonary flow occurred at the expense of systemic flow.

Lowering of pulmonary arterial pressure and resistance never occurred earlier than 20 minutes after the injection of serpasil. No attempt was made to investigate the effect of larger doses or to observe the duration of the effect. In no case did the patients experience any discomfort following the injection of serpasil.

Discussion

In mitral stenosis, administration of 1 mg. of serpasil resulted in a significant decrease of pulmonary arterial pressure, pulmonary capillary pressure remaining unchanged. This indicates that while the level of pulmonary capillary pressure is due entirely—or nearly entirely—to anatomical and hydrodynamic factors, the level of pulmonary arterial pressure is significantly influenced by constriction of the pulmonary vascular tree. This vasoconstriction is at least in

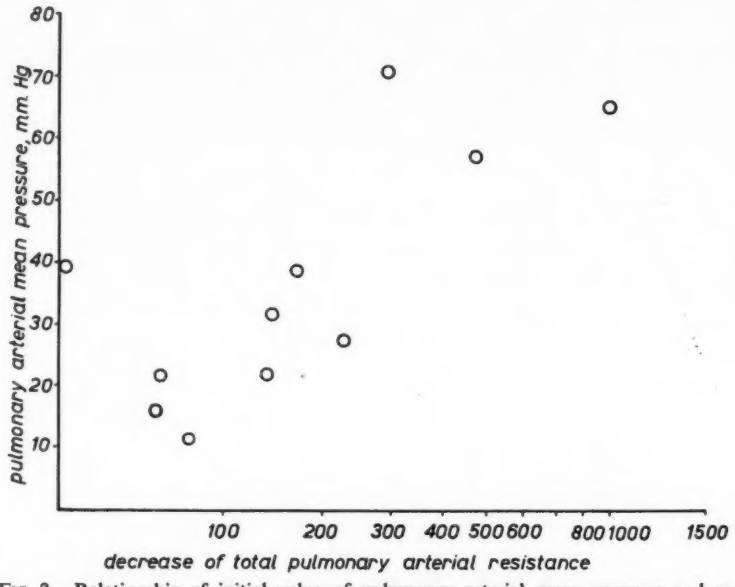

FIG. 2.—Relationship of initial value of pulmonary arterial mean pressure and serpasil-induced decrease of total pulmonary resistance.

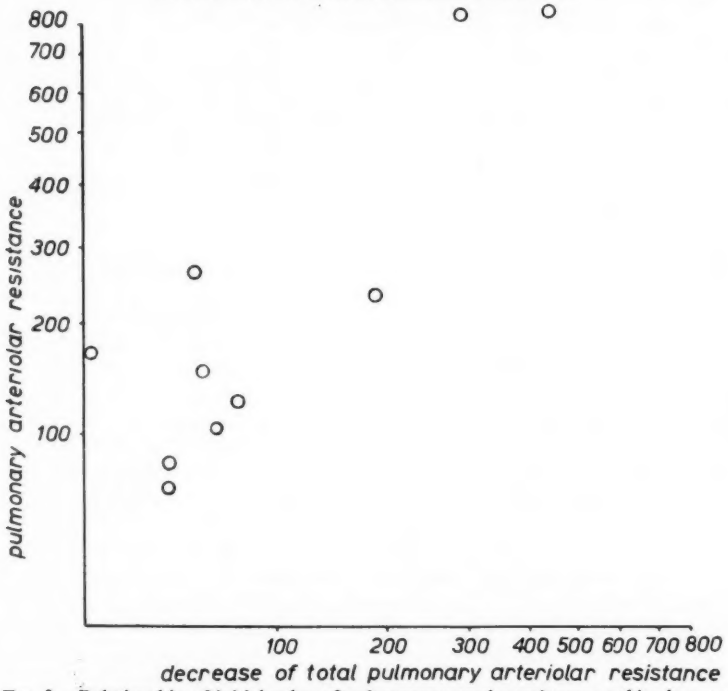

FIG. 3.—Relationship of initial value of pulmonary vascular resistance and its decrease following the administration of serpasil.

part inhibited by serpasil. If pulmonary arterial pressure is normal, as in our case of pulmonary stenosis (Table I, Case 2), or if pulmonary hypertension is due to an increased flow, as in our case of patent ductus arteriosus (Table I, Case 4), serpasil remains ineffective.

The remarkable drop of pulmonary arterial pressure and resistance in a case of ventricular septal defect may have important physiological and therapeutic implications.

Pulmonary vascular resistance may increase tremendously in some cases of congenital heart disease. This increased resistance in the lesser circuit is generally presumed to be a consequence of organic obliteration of the pulmonary vascular tree. These patients respond very poorly to surgical correction of the underlying anomaly: they have to be treated conservatively. Injecting acetylcholine in a patient suffering from patent ductus arteriosus with pulmonary hypertension, Harris (1955) observed a great fall in pressure in the pulmonary artery. A similar effect was obtained in this disease following the administration of priscoline by Denoline *et al.* (1952) and London *et al.* (1955). Priscoline given to a patient with atrial septal defect complicated by pulmonary hypertension resulted in a large decrease of pulmonary vascular resistance and an increase of pulmonary pressure and flow (Dresdale *et al.*, 1954). It seems therefore that pulmonary hypertension in the above types of congenital heart disease is due at least in part to vasoconstriction controlled by the nervous system. Further work is needed to elucidate the real significance of serpasil in the treatment of these conditions.

The extent of serpasil-induced decrease of pulmonary resistance was in most cases proportional to the initial level of pressure and resistance in the lesser circulation. This relationship is illustrated in Fig. 2 and 3. The appearance of a beneficial effect may be expected therefore especially in severe cases of pulmonary hypertension.

It remains uncertain whether unresponsiveness to serpasil, as in our Cases 7 and 12 is due to real drug-resistance or simply to insufficient dosage. As mentioned before, Case 12 died following valvotomy. Scott *et al.* (1955) advanced the hypothesis that a significant fall in pulmonary artery pressure after administration of tetraethylammonium chloride in a patient with mitral stenosis preoperatively is a good prognostic sign.

Serpasil had in our cases a remarkably elective effect on the lesser circulation. This was especially striking in our case of ventricular septal defect with pulmonary hypertension (Case 13). This is, however, in no way contradictory to earlier observations and means only that serpasil—as well as other hypotensive substances—acts mainly on constricted vessels irrespective of their belonging to the systemic or pulmonary circulation.

The pulmonary hypotensive effect of serpasil appears 20–30 minutes following its intrapulmonary administration. This long latency does not speak in favour of a direct vascular action. It is suggested that serpasil exerts its action by influencing the nervous system. A further possibility is that the action on the lesser circulation is not from serpasil itself but from one of its metabolites. A paper by Angelino and Levi (1956), who also observed a fall in pulmonary arteriolar resistance after the administration of serpasil in cases of mitral stenosis, has come to our notice since this paper was submitted.

Summary

The effect of the parenteral administration of 1 mg. of serpasil was investigated in subjects suffering from pulmonary hypertension.

In mitral stenosis a significant decrease of pulmonary arterial pressure, pulmonary vascular and total pulmonary resistances occurred. Pulmonary capillary pressure, and systemic arterial pressure and resistance remained unchanged.

A 50 per cent lowering of pulmonary arterial pressure and resistance occurred in a case of ventricular septal defect with pulmonary hypertension.

Systemic arterial pressure and resistance, being initially normal in all patients of this series, remained uninfluenced by serpasil. The drug acted in these cases exclusively on the lesser circulation, i.e. on that part of the vascular bed in which vasoconstriction existed.

As it may be given by mouth, and as it is fairly well tolerated, serpasil may have some therapeutic significance in certain cases of pulmonary hypertension.

Our thanks are due to Messrs. Ciba, Basle, for a generous supply of serpasil. Miss I. Szabó rendered invaluable help and assistance throughout these experiments.

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NETWORKS IN THE RIGHT SIDE OF THE HEART

BY

G. AUSTIN GRESHAM

From the Department of Pathology, University of Cambridge

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Delicate networks occur in the right side of the heart at three sites: at the entry of the inferior vena cava into the atrium, at the mouth of the coronary sinus, and between the endocardial surfaces of the right ventricle. The first clear account of the fenestrated valve of the inferior vena cava and coronary sinus was by Eustachi (1563, quoted by Franklin 1948). Franklin (1948) has reviewed the historical background of these valves and the theories concerned with their origin and function. Chiari (1879) described networks formed from the valves of the inferior vena cava, and in some cases of the coronary sinus, which showed attachments beyond the usual territories of these valves. These reticular formations are now called Chiari networks. Chiari himself considered them to act as a source of pulmonary emboli. Yater (1929) suggests that they may serve as a filter for emboli arriving at the right atrium from elsewhere in the venous system. This investigation is mainly concerned with the view that the network may act as a short circuit from sinu-atrial node to atrio-ventricular bundle.

Hearts from 300 consecutive necropsies were examined for the presence of networks in the right atrium and in the right ventricle. Of these 260 were from adults, 23 of whom were below the age of fifty; 7 were from children in the first five years of life; and 33 were from stillbirths and neonates.

RESULTS

In 58 of all hearts examined, of which 38 were from children of five years or less, no valves were found of either the coronary sinus or the inferior vena cava. In 204 of 260 adult hearts examined the commonest findings were along the lateral border of the coronary sinus and in order of frequency could be divided into: (*a*) a conspicuous crescentic valve flap often fenestrated, (*b*) a valve flap that completely covered the orifice of the coronary sinus and was adherent to its medial wall except at one or two points, and (*c*) a single strand which was present alone in 25, or in association with a fenestrated valve of the inferior vena cava in 9 (Fig. 1). If the inferior sinus septum (Fig. 1) was absent or poorly developed, then the strands were continuous with a fenestrated valve of the inferior vena cava in five cases (Fig. 2).

The next most frequent abnormality found in 75 cases was a fenestrated valve of the inferior vena cava (Fig. 1). In four cases the attachments of this valve extended up to the internal orifice of the superior vena cava and inferiorly to the atrioventricular ring near the site, anterior to the coronary sinus, of the atrioventricular node (Fig. 3). Such a valve with these attachments is called the Chiari network (Yater, 1929). Evidence will be presented to support the desirability of distinguishing it from a fenestrated valve of the inferior vena cava without such attachments.

The degree of fenestration of the valve of the inferior vena cava was variable. The simplest form was a fleshy crescentic valve with a few holes in its free border (Fig. 1) whereas the extreme degree of fenestration was the Chiari net.

In eight hearts a network was found closely applied, and for the greater part adherent, to the postero-inferior part of the fossa and annulus ovalis (Fig. 4). Finally networks were found joining

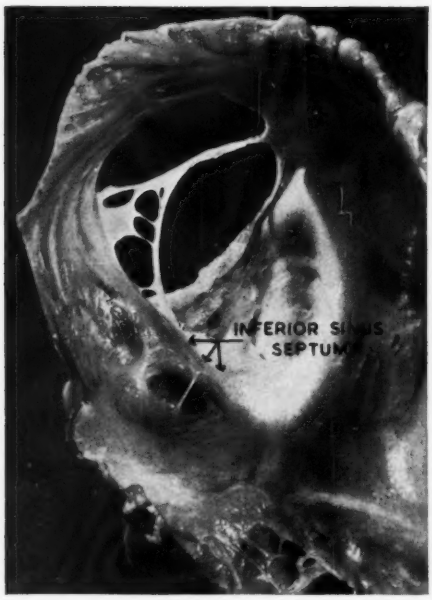

FIG. 1.—Fenestrated valve of the inferior vena cava (I.V.C.) and strand-like valve of coronary sinus.

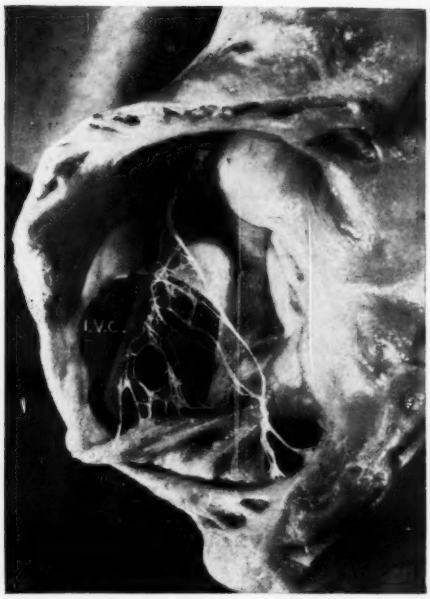

FIG. 2.—Continuity of valve of I.V.C. and coronary sinus due to absent inferior sinus septum.

FIG. 3.—Network of Chiari stretching across the opening of the I.V.C. into the atrium.

FIG. 4.—Remnants of the left valve of the sinus venosus on the medial wall of the right atrium.

the lateral wall of the right ventricle to the ventricular septum in 31 cases; these are usually situated towards the base of the heart and are not significantly associated with either presence or absence of the moderator band of the ventricle (Fig. 5).

Sections were prepared of atrial and ventricular networks and stained with hæmatoxylin and eosin and by Weigert's resorcin fuchsin method for elastic tissue. Strands of cardiac muscle were found in all networks (Fig. 6) and were surrounded by strands of elastic tissue, a feature noted by

FIG. 5.—Delicate strands crossing the right ventricle.

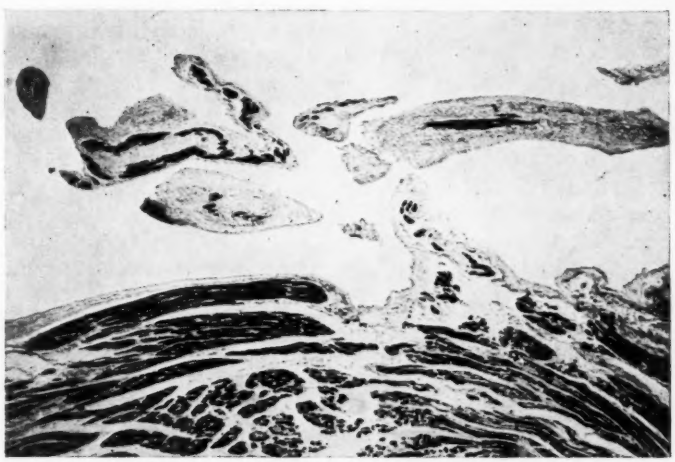

FIG. 6.—Strands of cardiac muscle in the network of Chiari (× 20).

Benninghoff (1930, quoted by Franklin, 1948). In a study of the conducting system of 94 hearts the author has also noted this close association of elastic fibres with the conducting tissue particularly of the sinu-atrial node and of the Purkinje branches in the ventricles; he considers it to be a more useful means of identification of the tissue than the morphology of the fibres themselves.

The following three case reports illustrate the part which these networks may play in disease.

Case 1 (F. 78). Admitted to hospital with seven days' history of anorexia and five days' pain in the right illiac fossa. A laparotomy was performed and the vermiform appendix removed. Six days later she became comatose, developed a right hemiplegia, and died.

Necropsy. Coiled thrombi were found in the right and left main pulmonary trunks. Recent thrombi were found in veins of the right calf. A recent thrombus filled the left common carotid artery and its internal carotid branch up to the middle cerebral artery. The brain showed a recent left cerebral infarct and a recent infarct was present in the right kidney, which was surrounded by an abscess containing 20 ml. of pus.

The significant findings in the heart were a patent foramen ovale (about 12 mm. in diameter) and a Chiari network in which was tangled ante mortem thrombus (Fig. 7).

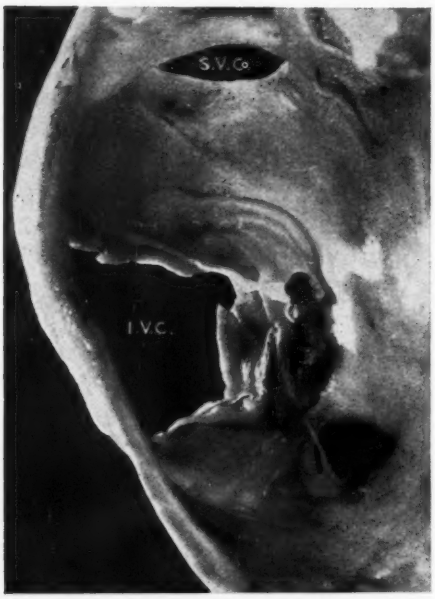

FIG. 7.—Recent thrombus tangled in the valve of the inferior vena cava.

Case 2 (F. 46). Suffered from attacks of dyspnœa for the four weeks before admission to hospital. One week before she had a severe attack while walking home. Cough had been present for one week. On examination she was found to be orthopnœic and deeply cyanosed. The neck veins were engorged to the angle of the jaw when sitting upright. An electrocardiogram taken on the third day after admission showed evidence of a recent pulmonary embolus with enlargement and peaking of P waves. An interesting feature was the variation in P–R interval.

Following three successive attacks of dyspnœa with loss of consciousness, the patient died on the fourth day after admission.

Necropsy. Old adherent thrombus filled the left main pulmonary artery and more recent thrombus the right. Moderately old thrombus filled the left iliac, popliteal, and tibial veins.

The relevant finding in the heart was a Chiari network (Fig. 8) extending from the site of the sinu-atrial node to a point just anterior to the atrio-ventricular node. The foramen ovale was valvular (about 0·5 cm. diameter).

Case 3 (F. 66). Found dead at home. There was no history of previous ill-health.

Necropsy. A recent antero-lateral and anterior septal cardiac infarct was present. A Chiari network was found in the right atrium (Fig. 3). A recent thrombus was found in the branch of the pulmonary artery to the right lower lobe. This was most probably embolic though no source of thrombi could be found in either leg veins or in the heart itself.

Comment. These three cases illustrate the inadequacy of the Chiari net as a filter for pulmonary emboli. One embolus by becoming entangled in it, completely destroys its filtering effect and allows further emboli to enter the pulmonary artery and also to pass through a patent foramen ovale (Case 1).

The variation of the P–R interval in Case 2 is most probably due to a shifting pacemaker, but could also be explained by supposing that the Chiari net provided an alternative path for the cardiac impulse.

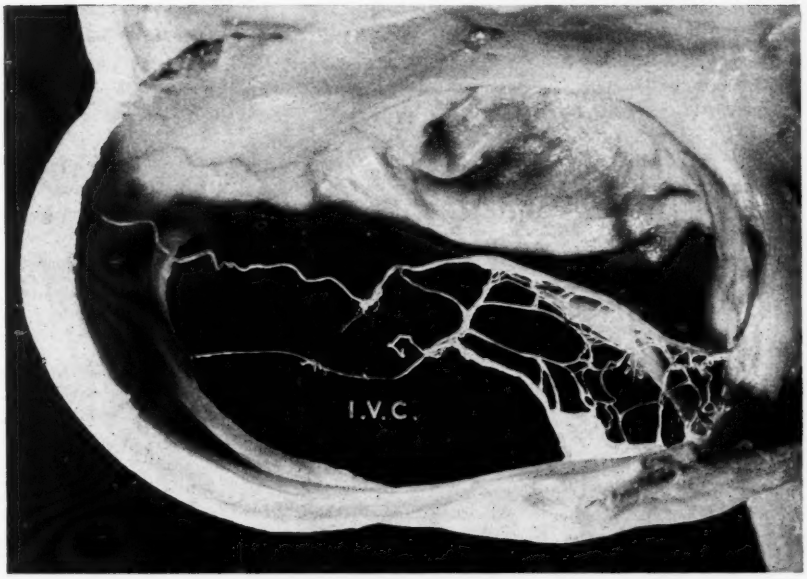

FIG. 8.—Chiari net, showing strands extending from the region of the S.A. node (on the left) to region of A.V. node (on right).

DISCUSSION

These networks present problems concerning their source of origin and their functional significance. Of the 30 hearts from children and infants, only one, an anencephalic, showed a valve of the inferior vena cava and yet in the adult hearts some sort of valve was found in 57 out of 260. It is difficult to believe that fenestrated valves of the inferior vena cava arise as a result of degeneration in previously intact valves. The valve of the inferior vena cava and the networks on the medial wall of the right atrium (Fig. 4) are now considered to arise from the right and left lips of the sinus venosus in the embryo. Their origin from atrial wall is supported by the finding of cardiac muscle fibres in their substance, but the discrepancy between the findings in the child and in the adult are difficult to explain except on the basis of the altering relationships of cardiac structures with growth. Such a discrepancy may not be of statistical significance in the present series and is also open to the criticism that these delicate structures may have been overlooked in the small infant heart. Such oversight can be prevented by dividing the inferior vena cava close to its pericardial reflection when removing the heart, so that the valve is not cut across, and also by teasing the orifice of the vena cava under a gentle stream of water so that the valve, if it has rolled up into a strand, will unravel and become visible. Such precautions were taken in all the cases examined in this series.

Various views have been expressed about the function of these networks. It has been considered that the valve acts mechanically by preventing blood from the superior vena cava entering the inferior vena cava, or in fœtal life by directing inferior caval blood through the foramen ovale. There is little evidence to support the idea that they may act as a source of or a filter for pulmonary emboli. Chiari's first case of a young man dying with pulmonary embolism, the only source of which was the atrial network, is insufficiently documented. The two cases quoted here illustrate the inadequacy of the network as a filter for emboli since the first embolus to become entangled in it renders it ineffective for further emboli.

Another idea that this network may conduct the cardiac impulse was initiated by Gatzi (1929) who described Purkinje tissue in them. Jordan (1926) suggested that it might serve as a path for the wave of atrial flutter.

The differentiation of Purkinje tissue from cardiac muscle is difficult (Glomset and Birge, 1948). The presence of elastic strands around each Purkinje fibre and around groups of fibres has been a distinguishing feature in the author's unpublished series. Such fibres were found at sites where conducting tissue was seen in the heart of an ox in which conducting tissue is easily differentiated from cardiac muscle. Field (1951) has revived the view that the conduction of the cardiac impulse is by nerves alone; it has not, to date, been possible to refute this idea and is as reasonable an explanation of the conduction of the cardiac impulse as is the conducting system itself. Purkinje tissue was not found in sections of networks, but cardiac muscle and nerve fibres were found. They may, therefore, provide an alternative path for the cardiac impulse from sinu-atrial node to atrio-ventricular bundle, or even to the septal muscle itself.

The variations of P–R interval in Case 2 could be explained by conduction down the Chiari net which linked the region of the S-A node to the atrio-ventricular bundle. The QRS complexes were not unduly broadened so that one may assume that ventricular excitation was normal. Such a network may in part explain the syndrome of Wolff, Parkinson, and White; opportunities to test this hypothesis at necropsy are rare. The varying tension that may develop in the network with changing venous pressure in the atrium would also provide a more feasible explanation of the intermittent character of the conduction defect than does the bundle of Kent which runs over the atrioventricular ring, the least distensible part of the heart.

The significance of the presence or otherwise of a valve of the coronary sinus is obscure. The delicate strands crossing the right ventricle may play a part in cardiac function as a conducting tissue; Tawara (1906) has described tendon-like strands containing conducting tissue crossing the cavity of the left ventricle.

It seems desirable to retain the term Chiari network for those valves of the inferior vena cava having attachments near the sinu-atrial node and along the course of the atrio-ventricular bundle, as they may play a part in short circuiting the atrio-ventricular node and provide a path for the atrial impulse which is shorter than that normally followed.

Summary

The incidence of networks in the right atrium and ventricle in 300 hearts is reported.

These networks contain cardiac muscle and may provide an alternative path for the passage of the impulse from sinu-atrial node to ventricle.

I am grateful to Dr. A. M. Barrett for his constant encouragement and to my colleagues Drs. A. G. Ackerley, B. Beeson, H. Middleton, and D. R. Winstanley for their assistance in the collection of material. I am indebted to Miss S. Westoby for the photography. Fig. 1, 2, and 5 are published by kind permission of the Editor of the British Journal of Photography.

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MALIGNANT AURICULAR ARRHYTHMIA

BY

WILLIAM DEWHURST

From the Cardiac Department of the London Hospital

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Abnormal foci in the auricles, from which the cardiac impulse may arise, beget various types of arrhythmia. Three main groups may be distinguished, namely, ectopic beats, auricular tachycardia (of slower or faster rate), and auricular fibrillation. Although the deranged auricular function is fundamentally similar in each variety, there are reasons for regarding the groups as separate nosological entities; the ætiology, clinical presentation, prognosis, and response to treatment differ, justifying the preservation of this clinical classification.

The benign nature of extrasystoles and of most instances of auricular tachycardia is known, and the more serious prognosis connected with some instances of auricular tachycardia and with auricular fibrillation is related to the underlying heart disease.

The purpose of this paper is to describe a syndrome that was found in four patients all of whom exhibited an arrhythmia different in form and course from the common varieties. Having regard to the serious prognosis identified with this condition the term *malignant auricular arrhythmia* is proposed for it.

Case Histories

Case 1. A woman, aged 67, who gave no relevant history of heart disease amongst her relatives, began to complain of attacks of palpitation and nocturnal breathlessness twelve years before. Nine years later she developed dyspnœa on effort followed by œdema of the legs. There was no history of cardiac pain, thyroid trouble, or rheumatic fever. When first seen, at the age of 56, she was obese, breathless, and had some œdema of the lower limbs associated with varicose veins. Crepitations were present at both lung bases, but the liver was not enlarged. The blood pressure varied from 150/100 to 120/90. The pulse was rapid (ventricular rate 120 a minute) and pulsus alternans was present. The electrocardiogram showed nodal tachycardia. The heart sounds were normal and there were no murmurs. Screening revealed a slightly enlarged left ventricle and hilar congestion.

She was given mecholin that day. On the next day there was a short period of auricular flutter followed by sinus tachycardia. One day later the nodal tachycardia had returned. In each case the nature of the arrhythmia was confirmed by electrocardiography. Treatment with quinidine was followed by transient episodes of sinus tachycardia. Digitalis was then given and was followed by normal rate and rhythm.

Subsequently she only had short attacks of palpitation. Four years later, however, dyspnœa on exertion and paroxysmal nocturnal dyspnœa returned. When seen her pulse was 140 a minute with pulsus alternans. The electrocardiogram taken during a period of sinus rhythm showed left ventricular preponderance and electrical alternation. Screening showed greater left ventricular enlargement and aortic unfolding. The hilar shadows were dense. Treatment with digitalis, mercurial diuretics, and bed rest was again followed by clinical improvement.

At the age of 65 dyspnœa on exertion returned and was accompanied by hæmoptysis, œdema, orthopnœa, and paroxysmal nocturnal dyspnœa, in that order. She also complained of a pressing feeling under her left breast which bore no relation to exertion. When seen three months later she had ankle and sacral œdema but the venous pressure was normal. The blood pressure was 145/85 and a soft systolic murmur was audible at the apex. Cardioscopy revealed moderate cardiac enlargement mainly involving the left ventricle. Clinical and electrocardiographic examination had shown auricular fibrillation, extrasystoles, auricular tachycardia with 2–1 A-V dissociation, and sinus rhythm, at different times (Fig. 1). Continued treatment with digitalis and the addition of mercurial diuretics was followed, after several days, by a reversion to sinus rhythm, and the signs of heart failure regressed.

She continued to have dyspnœa and her pulse was irregular from extrasystoles while the blood pressure remained normal. Twelve years from the start of her illness she was admitted to hospital with cardiac asthma. The rhythm at the time was irregular from auricular fibrillation and radiological examination again showed enlargement of the left ventricle, hilar congestion, and slight left hydrothorax. She subsequently died.

FIG. 1.—Case 1. Sinus rhythm in CR1 (A), extrasystoles in lead II (B), auricular tachycardia in lead I (C), and auricular fibrillation in CR1 (D).

FIG. 2.—Case 2. Lead CR1, showing sinus rhythm (A), extrasystoles (B), auricular tachycardia (C), and auricular fibrillation (D). Partial right bundle-branch block.

At necropsy there was considerable hypertrophy and moderate dilatation of the left ventricle, and slight hypertrophy and dilatation of the right ventricle and of both auricles. The heart weight was 18½ oz. (544 g.). There was insignificant thickening of the free margin of the mitral valve which caused no deformity. The aortic valve was normal. Serial sections of the left ventricle including the interventricular septum showed no myocardial abnormality apart from hypertrophy. There was no evidence of myocardial fibrosis, nor of cardiac infarction. Injection of the coronary arterial tree by an opaque substance showed a plentiful system of vessels to all parts of the heart. Sections stained with Congo Red showed no amyloid. There was a thrombotic embolus in one of the branches of the pulmonary artery supplying the right lower lobe: no source of the embolus was found. The endocrine glands appeared normal.

Case 2. A man, aged 65 years, who gave no previous history of rheumatic fever or family history of heart disease, had remained well until seven years before when he complained of his first attack of palpitation. The attack had started suddenly and the heart action was irregular during the eight hours that elapsed before it gradually stopped. He subsequently experienced two bouts of rapid regular beating lasting 3½ and 1½ hours respectively.

When examined the pulse was 80 a minute and was regular. The blood pressure was 160/80. There was a faint systolic murmur at the apex. There was no cardiac enlargement.

Two years later the attacks of palpitation returned, lasting about an hour, and with sudden onset but gradual cessation. The painless attacks associated with breathlessness continued during the next twelve months uninfluenced by quinidine. When re-examined he showed auricular tachycardia and was admitted to hospital. The heart action varied between sinus rhythm and auricular tachycardia which could be stopped by carotid sinus pressure. The blood pressure was 140/80. Auscultation showed neither added sounds nor murmurs and this was confirmed by phonocardiography. The electrocardiogram taken during sinus rhythm showed S–T depression in the standard limb leads and in V4 to V6. Digitalis had not been given at this stage.

After leaving hospital he continued to have frequent attacks of palpitation during the next twelve months which could not be controlled by either digitalis or quinidine. The electrocardiogram showed, at various times, sinus rhythm, extrasystoles, and auricular tachycardia (Fig. 2). On one occasion, after several severe attacks of arrhythmia, the electrocardiogram also showed evidence of cardiac ischæmia (in addition to digitalis effect) which subsequently recovered (Fig. 3).

Five years from the onset the heart showed moderate generalized enlargement on screening. Palpitation continued unabated and electrocardiograms taken during some of the bouts all showed auricular tachycardia. Later the patient developed dyspnœa on exertion, and swelling of the ankles, and presented the signs of congestive heart failure with considerable cardiac enlargement. The electrocardiogram now showed auricular fibrillation (Fig. 2D). Treatment with digitalis and diuretics was followed by improvement. He continues, however, to suffer from palpitation and still remains under medical supervision. His pulse varies from sinus rhythm to auricular tachycardia or auricular fibrillation, with or without extrasystoles. The blood pressure is 150/80 and the heart sounds normal. The Wassermann reaction is negative. He continues to be orthopnœic and cardioscopy shows persistent general cardiac enlargement and hilar congestion.

Case 3. A man, aged 62 years, had never suffered from rheumatic fever and his family history did not uncover any relevant illness in his family. At the age of 47 he experienced his first attack of palpitation which was of sudden onset and lasted four hours. It was accompanied by a choking sensation in the throat but no frank pain. He subsequently had attacks usually lasting 1½ hours. At the age of 55 he had a further severe attack of palpitation which was associated on this occasion with chest pain. Clinical examination revealed no abnormal signs and the blood pressure was 135/95. The electrocardiogram was normal and showed no evidence of cardiac infarction. The heart was not enlarged when examined radiologically. Two years later he had further short severe attacks of palpitation associated with tightness in the chest and of 10 minutes duration. A cardiogram showed auricular tachycardia (Fig. 4B). Treatment with quinidine was followed by a reversion to sinus rhythm after five hours. A further attack five months later lasted for four hours. The electrocardiogram then showed auricular fibrillation (Fig. 4C). Treatment with digitalis for two weeks had little effect on the attacks. On one occasion he was admitted after a severe bout of palpitation, again with tightness in the chest, and cardiac infarction was simulated but the cardiogram showed fibrillation and no evidence of infarction. In the intervals between paroxysms of arrhythmia he was free from symptoms and never had any chest pain: the cardiogram also was normal. At the age of 59, however, radiological examination of the heart showed that it was now slightly enlarged. Attacks of palpitation continued, and these were now exclusively rapid auricular fibrillation which proved unresponsive to digitalis. When aged 61 paroxysmal nocturnal dyspnœa set in and cardioscopy showed pulmonary congestion and generalized enlargement, mostly of the left ventricle. Quinidine had no effect on the rapid fibrillation and digitalis was only slightly more satisfactory. At his last attendance the dyspnœa on effort had greatly reduced his activities. Examination revealed rapid auricular fibrillation, normal heart sounds, and a soft systolic murmur at the base of the heart; the blood pressure was 110/70. The Wassermann reaction was negative. Cardioscopy showed generalized cardiac enlargement, mainly involving the left ventricle, and some emphysema (Fig. 6).

Case 4. A man, aged 47, with no previous history of rheumatic fever, had remained well until two years before when he presented with difficulty in taking a satisfactory breath. On examination he was of normal nutrition, but had a moderately severe kyphosis, a fixed chest, and diminished diaphragmatic movement. His pulse was 70 a minute and regular, and there was no hypertension, but his doctor had noted over the years that sinus tachycardia and extrasystoles could easily be provoked and that his blood pressure was labile. The electrocardiogram showed nothing except the effect of digitalis which he had taken for six weeks without benefit.

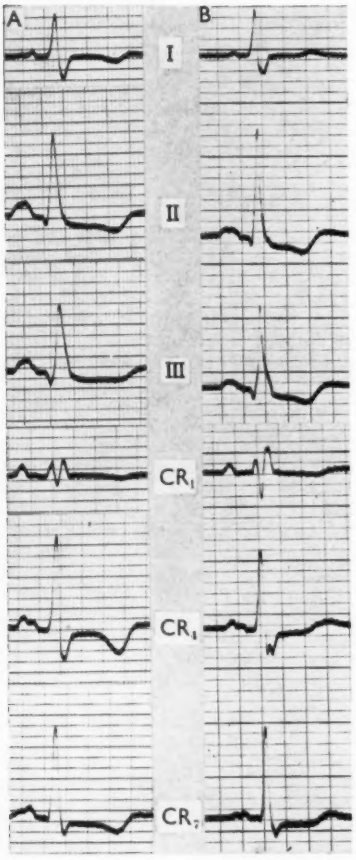

FIG. 3.—(Case 2). Ischæmic changes (A) following severe attacks of arrhythmia with recovery in (B) except for digitalis effect.

A month later he was admitted to hospital complaining of dyspnœa, palpitation, and a dry cough. His heart rhythm varied from sinus tachycardia to extrasystoles and auricular fibrillation. There was no hypertension or evidence of valvular disease. The X-ray at this time showed moderate cardiac enlargement mainly involving the left ventricle. The cardiogram also showed early signs of left ventricular hypertrophy. Treated with digitalis and also with thiouracil he improved for a time and was discharged from hospital but dyspnœa then recurred and was associated with palpitation.

Examination revealed œdema of both lower limbs, enlargement of the liver, and a raised jugular venous pressure. The cardiogram showed, at different times, sinus rhythm, ectopic beats, and auricular tachycardia. Generalized cardiac enlargement was present at cardioscopy (Fig. 7). A radioactive iodine test performed after thiouracil had been stopped for six weeks was normal. Treatment with digitalis, a low sodium diet, and mercurial diuretics, had little beneficial effect and the paroxysms of arrhythmia were quite uninfluenced by any form of treatment. He was readmitted to hospital two months later, at the age of 47, complaining of greater dyspnœa and palpitation. There was no history of pain, nor nocturnal dyspnœa, now, or at any other time during the illness. When examined there was a raised jugular venous pressure and rapid venous waves suggestive of auricular tachycardia. There was moderate sacral œdema, and fine crepitations were present in the lungs. The pulse was 120 a minute and regular. The rate was halved following carotid sinus pressure. An auricular sound was heard at the apex, but the heart sounds were otherwise normal and there were no murmurs. Treatment had little effect. He was also given ansolysen because his blood pressure was found to be raised for the first time and was 180/130. This was followed by a fall in pressure to normal limits but two weeks later he developed a purpuric rash followed by polyarthritis, so all drugs except digitalis were stopped without any change in his condition. The cardiac rhythm continued to move from sinus rhythm to auricular tachycardia and auricular fibrillation (Fig. 5). Full hæmatological studies were carried out and included estimations of hæmoglobin, white blood cells, eosinophils, platelets, reticulocytes, serum albumin and globulin, prothrombin activity, blood culture, ascorbic acid saturation test, coagulation time, and capillary fragility; they all gave normal values. The Wassermann and Kahn reactions were both negative. No lupus erythematosus cells were found. The urine contained a cloud of albumin. The blood urea was 43 mg. per 100 ml. The ESR varied from 12 to 22 mm. an hour. Concentration and dilution tests showed good renal function. Muscle biopsy was negative. A course of cortisone was given, but it produced no improvement and he lapsed into coma and died. Terminally the heart rhythm was auricular fibrillation. Necropsy was refused.

CHARACTERISTIC FEATURES

The age at onset in the four patients, three men and one woman, was 58, 55, 47, and 45 years, respectively. The condition appears to be uncommon for no others have so far come to our notice.

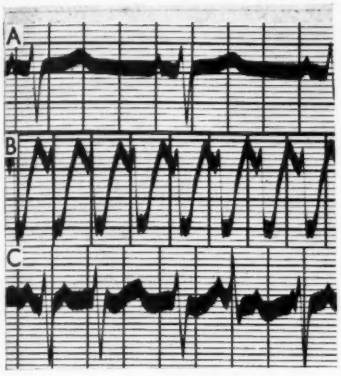

FIG. 4.—Case 3. Lead CR1 showing sinus rhythm (A), auricular tachycardia (B), and auricular fibrillation with extrasystole (C).

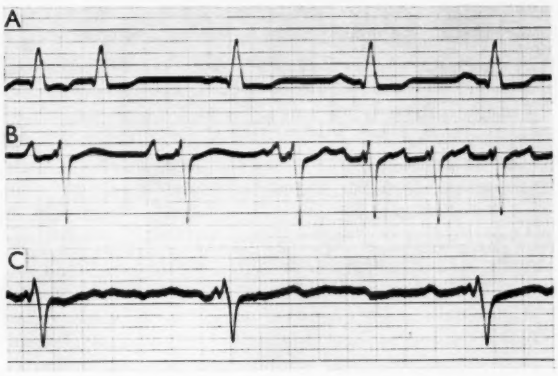

FIG. 5.—Case 4. Sinus rhythm and extrasystole in CR7 (A), sinus rhythm changing to auricular tachycardia in CR1 (B), and auricular fibrillation in CR1 (C).

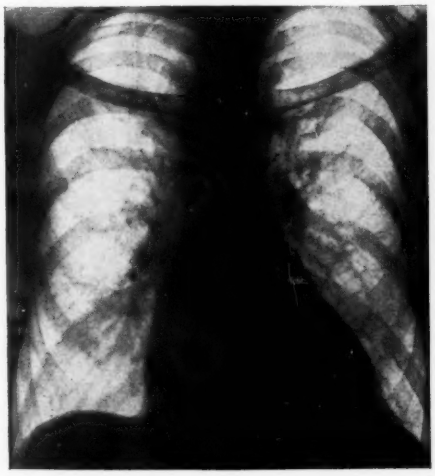

FIG. 6.—Case 3. Generalized enlargement of the heart and especially of the left ventricle. Much hilar congestion.

FIG. 7.—Case 4. Great generalized enlargement of the heart and especially of the left ventricle with considerable pulmonary congestion.

The Protean Nature of the Arrhythmia. A striking feature of all four cases was the extraordinary facility with which paroxysms of the separate kinds of auricular arrhythmia followed one another. This is in contrast with the more common varieties of auricular arrhythmia in which the majority of patients suffer from a single dominant disturbance the course of which can be forecast with some accuracy. In malignant auricular arrhythmia, however, one is faced with a mutable rhythm of an unpredictable and disorderly nature. Thus, in Case 1, the following paroxysms occurred in succession during the course of the illness: nodal tachycardia, auricular tachycardia, auricular extrasystoles, auricular fibrillation, and sinus rhythm. In Case 2 auricular tachycardia with slow

ventricular rate (flutter) alternated with auricular tachycardia with high ventricular rate which could be stopped by carotid sinus pressure, auricular fibrillation, and sinus rhythm. Case 3 showed paroxysms of auricular tachycardia (flutter), fibrillation, and sinus rhythm. Case 4 exhibited at different times, and in varying sequence, sinus tachycardia, extrasystoles, auricular tachycardia, and auricular fibrillation.

The Absence of Any Known Cause. In none of the cases was there any evidence of a known cause in the heart or elsewhere. Their out-patient attendances were numerous and they were, therefore, observed over long periods, both as out-patients and in-patients.

There was no evidence of thyrotoxicosis. Although it was suspected at one stage in Case 4 the radioactive iodine test was found to be normal while thiouracil had no effect on the arrhythmia nor on the unfavourable course of the illness.

Similarly, cardiac infarction could not be established as the cause nor was there any histological evidence of this in the case that came to necropsy. Case 3 experienced attacks of tightness in the chest during attacks of palpitation, but at no other time, and Cases 1, 2, and 4 gave no history of cardiac pain either during attacks of palpitation or during the intervals when they were in normal rhythm. The absence of pain in these cases does not, of course, rule out the diagnosis, for it is known (Evans and Sutton, 1956) that the onset of cardiac infarction associated with cardiac arrhythmia is commonly painless so that the diagnosis of infarction during life must rest primarily on the electrocardiogram. In this connection it is necessary to recognize that paroxysms of arrhythmia may by themselves cause temporary cardiac ischæmia with consequent cardiographic changes. Thus, in Case 2 there was T wave inversion at one stage that recovered rapidly. The effects of digitalis, also, may cause confusion. Bearing these factors in mind scrutiny of the electrocardiogram has shown no evidence of cardiac infarction as a cause in any of the four cases.

The ultimate presence of left ventricular enlargement in three of the cases directed particular attention towards a lesion of the aortic valve, but it was never found. The mitral valve was also normal. Hypertension, too, was sought but never substantiated. The highest recorded diastolic pressure at any time was 100, 90, and 95 mm. Hg respectively in Cases 1, 2, and 3: in Case 4 a raised blood pressure was noted as a terminal and temporary event, but during the greater part of the illness it was within normal limits. At the onset the electrocardiogram showed no left ventricular preponderance nor did radiology reveal left ventricular enlargement in any of the four cases. These changes only appeared after the paroxysms of arrhythmia had been present for some months. Nor was there any evidence of the rarer causes of myocardial disease such as cardiac amyloidosis, familial cardiomegaly, disseminated lupus erythematosus, and alcoholic cardiomyopathy.

Cardiac Enlargement and Failure. The interval between the onset of severe symptoms and the development of cardiac enlargement was 1, 5, 1½, and 1 year respectively in the four cases and the period between the onset of heart failure was 1, 6, 5, and 1 year. As the enlargement followed the onset of the arrhythmia it is clear that the latter cannot have resulted from a large heart. The reverse, perhaps, may be true. This secondary cardiac enlargement is an essential feature of malignant auricular arrhythmia and is the antithesis of familial cardiomegaly where the cardiac enlargement predisposes to extrasystoles, auricular tachycardia, or auricular fibrillation.

In Case 1, cardiac enlargement, mainly affecting the left ventricle, was first noted one year after the onset of symptoms, when left ventricular preponderance was present in the cardiogram. Increase in heart size was progressive but, apart from a transient episode at the onset of the arrhythmia, left ventricular failure did not set in until 11 years later; it then continued until her death. In Case 2 generalized cardiac enlargement was noted 4 years after the onset and a year later congestive failure occurred. The electrocardiogram showed partial right bundle-branch block. Cardiac enlargement and hilar congestion persist. In Case 3 cardiac enlargement did not occur until 12 years from the onset of minor attacks of palpitation but only one year after severe attacks of arrhythmia had set in. Heart failure occurred 3½ years later. As in Cases 1 and 4 the left ventricle was predominantly enlarged and the cardiogram showed left ventricular preponderance.

Case 4 showed cardiac enlargement a year after the onset: heart failure followed a month later and continued, with little remission, until his death. Again the left ventricle was predominantly affected.

Resistance to Therapy. The effect of treatment was uniformly disappointing. Digitalis and quinidine were given prolonged trials in all four cases but neither drug was of material use, either during a paroxysm or between attacks as a deterrent. Mecholin and antithyroid drugs were also given in Cases 1 and 4, with similar lack of success.

Prognosis. The prognosis in this condition is serious. Two patients have died twelve and four years after the onset. The remaining two have developed marked cardiac enlargement and are subject to recurrent heart failure. This ominous and progressively downward course is a distinctive feature, separating it from the other kinds of auricular arrhythmia. Thus, extrasystoles occurring in the absence of an organic cardiac lesion are benign. Auricular extrasystoles do not differ from the ventricular variety in this respect (Scherf and Schott, 1953). Auricular tachycardia, also, when arising in a healthy subject, carries a good prognosis. The oft-quoted case reported by Lewis (1937), of a clergyman who suffered from auricular flutter continuously for 24 years, also illustrates this benign outlook. Lone auricular fibrillation, similarly, does not shorten life for it does not give rise to cardiac enlargement or failure and does not require special treatment (Evans and Swann, 1954). Malignant auricular arrhythmia, therefore, stands apart among the other forms of arrhythmia which are relatively benign in the absence of heart disease, for it resists all forms of treatment and ultimately causes the death of the patient.

Diagnosis. The characteristic features that have been described should enable a diagnosis of malignant auricular arrhythmia to be made in the occasional patient who exhibits it. Three things in particular help in its recognition. First, the variability of the arrhythmia, so that within a relatively short time the rhythm may change from sinus rhythm to show successively, extrasystoles, auricular tachycardia of fast or slow rate (flutter), and auricular fibrillation. Second is the obstinacy that it shows to treatment. Third is the gradual development of left ventricular enlargement and the onset of heart failure.

The diagnosis can never be easy at the start of the illness in the first episode of arrhythmia, and a diagnosis of an innocent form is usually made at the time. Indeed, opinion on the benign nature of the condition has hitherto persisted until cardiac enlargement and failure have set in and a poor response to treatment has become evident. In future the erratic mutability of the heart rhythm which is the earliest recognizable phase of the condition should suggest the diagnosis of malignant arrhythmia.

Four conditions, in particular, may have to be entertained in differential diagnosis. Thus, *auricular fibrillation with high ventricular rate*, although rare, may persist for years without intermission at a ventricular rate of 130 to 160 a minute. These cases resemble malignant auricular arrhythmia in that both are resistant to treatment, but differ in that auricular fibrillation persists unchanged from the onset until death ensues. Further, this kind of fibrillation is associated with a serious organic lesion such as cardiac infarction, thyroid toxæmia, or untreated mitral stenosis, and these may often elude detection for a time. A deliberate search for these causes substantiates the diagnosis. *Persistent auricular tachycardia* very occasionally lasts for months or years. It may thereby be mistaken for malignant auricular arrhythmia, particularly if there is no apparent cause for the tachycardia, and heart enlargement and failure have set in. The fact that auricular tachycardia remains as the constant dominant arrhythmia enables the condition to be distinguished from malignant arrhythmia. *Cardiomegaly with subsequent arrhythmia* may also confuse the diagnosis. Thus, in familiar cardiomegaly, extrasystoles, auricular tachycardia, and auricular fibrillation may all occur (Evans, 1949). The distinction rests with the appearance first of cardiac enlargement which is considerable before the arrhythmia sets in. In malignant auricular arrhythmia precisely the reverse holds true. The more obscure forms of cardiomyopathy will similarly cause difficulty in diagnosis, although the tendency in these to show mutability of rhythm is not as great as in malignant auricular arrhythmia. *Lone auricular fibrillation* differs in important respects from malignant auricular arrhythmia. Although found in the same age group, and without demonstrable

cause, it seldom causes difficulty in differential diagnosis for, as Evans and Swann (1954) have held, the ventricular rate is never rapid, cardiac enlargement and symptoms and signs of heart failure are never present, and it carries an excellent prognosis.

Mechanism and Ætiology. That cardiac enlargement follows the arrhythmia has already been stressed, but the mechanism by which this occurs is obscure. The most likely explanation appears to be that, during attacks of persistent, high rate, arrhythmia, the cardiac contraction becomes slightly incomplete. This leads to some accumulation of blood in the chambers with resultant overfilling. The muscle fibres respond to the stimulus of overstretching by hypertrophy.

The selective enlargement of the left ventricle is less easily explained. Daley *et al.* (1955) have found experimentally that functional mitral incompetence can accompany auricular fibrillation, and Müller and Shillingford (1954) have observed functional tricuspid incompetence during auricular fibrillation in man. Functional mitral incompetence (which may be due to retarded A-V valve closure and need not necessarily depend on cardiac enlargement or a dilated mitral ring), may be followed by left ventricular hypertrophy. Whether such a mechanism accounts for the left ventricular enlargement in the cases described must remain hypothetical. The absence of left ventricular enlargement in lone auricular fibrillation is probably due to the slow ventricular rate so that contractions, though irregular in timing, are each able to empty the ventricle completely.

The cause of the arrhythmia itself must remain speculative. By definition known organic disease is excluded. A disturbance of the autonomic system is unlikely on experimental grounds for direct stimulation alone rarely and inconstantly produces disordered rhythm. In view of the age of the patients a degenerative or ischæmic lesion appears to be the most likely cause. Although no gross infarction was found electrocardiographically or at necropsy it may well be that partial ischæmia of the auricular muscle, undetectable by present methods, may render it more likely to produce ectopic foci.

Summary

A syndrome is described in which a frequently changing heart rhythm eventually led, in spite of treatment, to left ventricular enlargement and heart failure. It occurred in four patients of middle age. In each the heart rhythm changed, often in quick succession, from sinus rhythm to auricular extrasystoles, auricular tachycardia of slow or rapid rate, and to auricular fibrillation. Two patients died.

No cause has been discovered following clinical, electrocardiographic, and cardioscopic examination in each patient, and necropsy in one. Because of its failure to respond to orthodox treatment and its serious prognosis the term malignant auricular arrhythmia is proposed for it.

I wish to thank Dr. William Evans who suggested this investigation and whose criticism and help were invaluable in the preparation of this paper. Mr. William Dicks assisted with the illustrations.

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FUNCTIONAL TRICUSPID INCOMPETENCE IN RELATION TO THE VENOUS PRESSURE

BY

CONRAD LOTTENBACH AND JOHN SHILLINGFORD*

From the Department of Medicine, Postgraduate Medical School, Hammersmith, London

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Observations on the right atrial pulse (Korner and Shillingford, 1954), right atrial blood flow (Müller and Shillingford, 1955), and dye circulation studies (Korner and Shillingford, 1955) have confirmed the clinical impression (Müller and Shillingford, 1954) that functional tricuspid incompetence is common in congestive cardiac failure where the venous pressure is raised to a mean level of 8 mm. of mercury above the normal average zero. Further observations on the tricuspid valve at necropsy have added confirmation to these findings and the purpose of this paper is to show that there is a relationship between the presence of an incompetent valve at necropsy and a grossly raised venous pressure during life, and to study the mechanism involved in the production of this incompetence.

Historical Note

In 1835, King placed in the museum of Guy's Hospital more than 300 specimens to illustrate the anatomy and function of the tricuspid valve. He published in 1837 a remarkable account of the tricuspid valve and suggested on anatomical grounds that it was responsible for regulating the right ventricular output by becoming incompetent if the right ventricle became dilated; this, in turn, would prevent overfilling of the pulmonary circulation.

His description of the valve is as follows, " The right atrioventricular opening is oval and to its circumference the membrane of the tricuspid valve has attachment without any distinct interruptions whilst its floating border, depending into the ventricle, is deeply fissured, so as to form three or more scalloped or angular curtains; and it appears, from careful examination, that the united areas of these valvular portions are scarcely more than equal to the mean extent of the oval opening. One of the curtains (which being least moveable, I have called fixed) occupies the left margin of the aperture in apposition with the solid wall from which arise all the cords that serve to secure the free edge and the ventricular surface of the fixed curtain. These cords are of such a length as scarcely to allow the curtain to rise into the plane of the oval opening in the natural play of the valve, and being destitute of muscular columns cannot, by any possibility, set the valve in motion or serve any other purpose than that of preventing too great a reflux of the curtain itself. A second curtain (the anterior) is attached at the anterior and right edge of the opening, having one free border and another backwards in the ventricle. Each border has its proper set of cords, the anterior or upper set have their insertion into a mere nipple of muscle on the solid wall, in the direction of the pulmonary artery; and the inferior or posterior are as invariably collected with numerous others into the summit of a muscular column whose base is inserted into the right or yielding wall of the ventricle near its centre . . . is frequently fissured. . . . Its cords are accordingly arranged in two or more sets, the greater part of which are attached by the intervention of muscular columns to the outer yielding wall at a considerable distance." (Then he goes on to describe it in great detail.)

METHODS AND MATERIALS

The hearts from 25 subjects were examined at necropsy in the routine way. Fifteen were from patients in whom there was no evidence of cardiac disease in life or at subsequent necropsy. Ten cases had evidence of congestive cardiac failure with a raised venous pressure in life and included chronic rheumatic (3), ischæmic (1), hypertensive (2), pulmonary (3), and anæmic (1) heart disease.

In addition a rubber tube was inserted through the intact pulmonary artery into the right ventricle. Water was allowed to flow gently through this and distend the right ventricle while the

* Member of Medical Research Council Scientific Staff.

whole heart was held in the hand under water. The behaviour of the tricuspid valve could then be watched through the opened right atrium. An incompetent orifice was measured and in addition photographs were taken by electronic flash in all cases. Although in the earlier cases an attempt was made to standardize the perfusion pressure it was found that this made photography impossible in some, due to the rapid regurgitant stream obscuring the field. In practice, gentle perfusion in no case gave more than the slightest incompetence in control hearts, whereas those who had congestive failure in life showed varying degrees of incompetence. Rigor mortis also affected the behaviour of the right ventricle and a high degree of physical accuracy is of course not possible in this test, but the results were clear cut in the majority of cases even allowing for the experimental error.

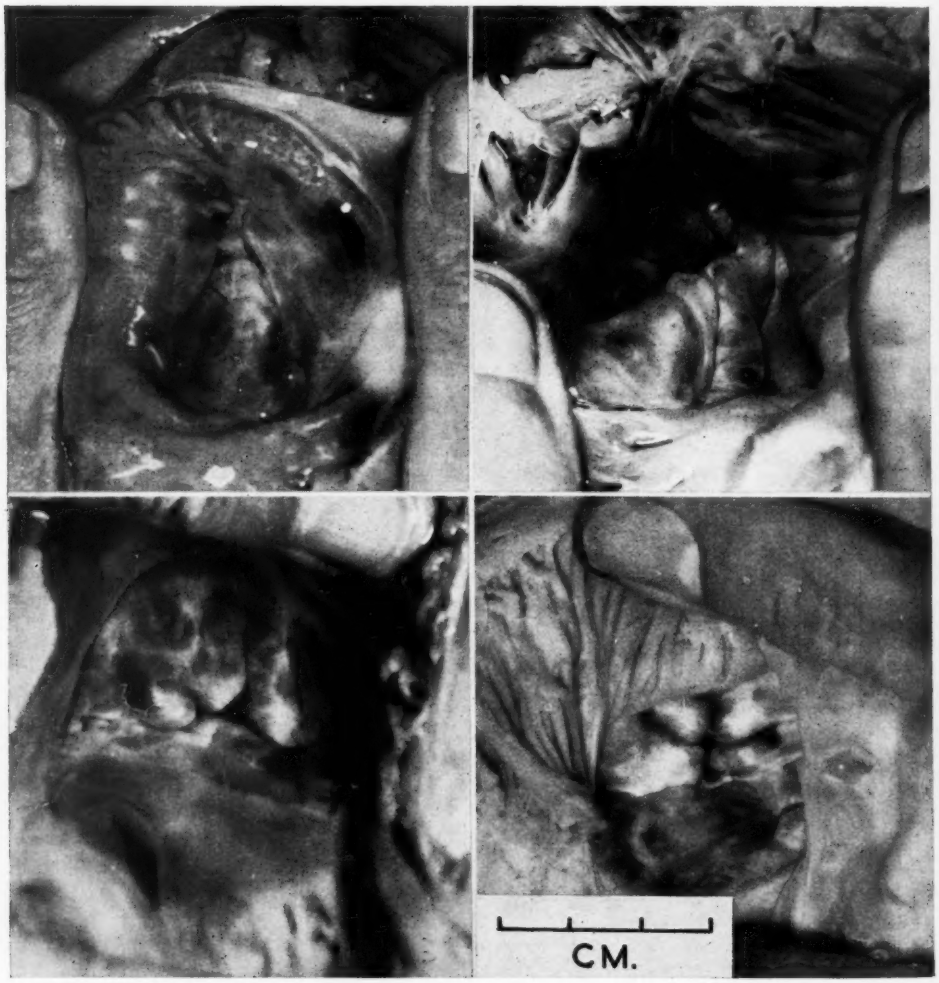

FIG. 1.—The perfused tricuspid valve photographed under water through the opened left atrium in four subjects without evidence of cardiac disease. The lower two show the maximum aperture of reflux found in the normal group.

Results

The fifteen hearts from subjects who had no heart disease in life all showed a competent tricuspid valve (Fig. 1); the three leaflets approximated along their free edges with no orifice at their centre. Increasing the pressure in the right ventricle caused a bulging of the cusps, and inversion of the edges at the point where the chordæ were inserted until, if the pressure were enough to dilate the ventricle considerably the valve would leak. Without dilatation of the ventricle, however, the normal valve appears to be watertight.

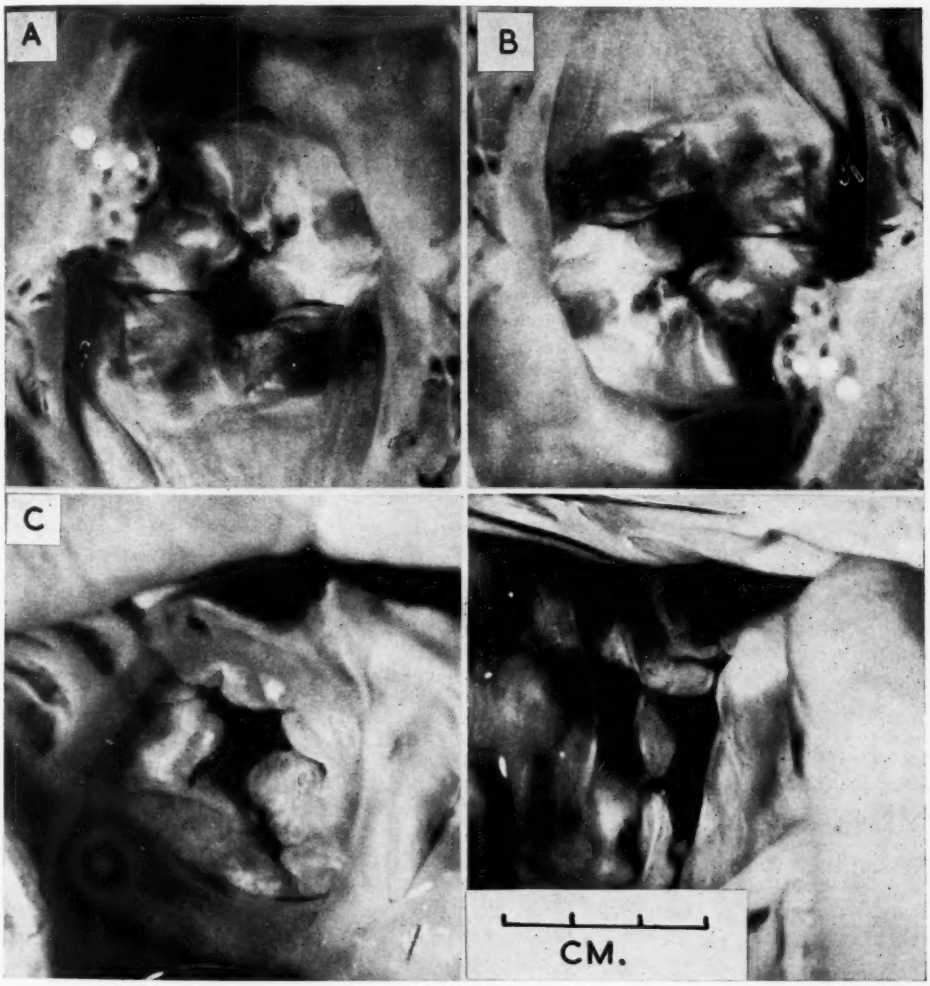

FIG. 2.—The perfused tricuspid valve photographed under water through the opened left atrium in four subjects all of whom in life had evidence of congestive cardiac failure and a raised venous pressure. (A) Ischæmic heart disease, terminal congestive failure with a grossly raised venous pressure. (B) Hypertensive cardiac failure with jugular venous mean pressure of 8 mm. Hg. (C) Severe anæmia secondary to myosclerosis with dilated heart and mean jugular venous pressure over 10 mm. Hg. (D) Chronic rheumatic heart disease and congestive cardiac failure with the mean jugular venous pressure over 10 mm. Hg.

In the cases in which, in life, there had been congestive cardiac failure, varying amounts of tricuspid incompetence were found by this test. The incompetence appeared to be produced by two different mechanisms, the first by a general dilatation of the right ventricle which pulled the chordæ attached to the edge of the valve in a downward and outward direction. This gave a funnel appearance to the valve (Fig. 2B); the second appeared to be a general dilatation of the valve ring. The size of the orifice varied from a few mm. in diameter up to 8 square cm., the latter being of greater area than the outflow tract of the pulmonary valve.

Discussion

Both King (1837) on anatomical grounds and Mackenzie (1904) on clinical observation emphasized the frequent occurrence of tricuspid incompetence in congestive heart failure. Recent work of our own has shown regurgitation to occur through the tricuspid valve in association with a rise in the mean right atrial pressure above the level of approximately 8 mm. of mercury. Although the technique employed for measuring the valve orifice at necropsy was the best that we could devise, there are obvious sources of error in assuming that these measurements applied in life. In spite of this the findings of valvular incompetence correlated with the clinical findings of a grossly raised venous pressure and congestive cardiac failure in life. The size of the tricuspid incompetent orifice in severe cases was as large as, or larger than, the outflow tract of the right ventricle and it is therefore apparent that the amount of regurgitant flow in these cases may equal or exceed the forward output of the right ventricle.

The mechanism of the production of incompetence is almost certainly due to dilatation of the right ventricle pulling down the chordæ in the first instance with dilatation of the valve ring developing later. Both mechanisms play a part in the long standing case. Increased filling of the right ventricle with greater dilating will produce a greater degree of incompetence; this is well seen in patients with functional tricuspid incompetence where increasing venous return by exercise or hepatic compression increases the size of the positive systolic wave in the jugular venous pulse. Decreasing the venous return to the ventricle allows the valve cusps to approximate more closely and reduce the regurgitant flow (Korner and Shillingford, 1957).

Summary

The tricuspid valve has been studied at necropsy in 25 subjects, 10 of whom had congestive cardiac failure in life.

In all cases of congestive cardiac failure in which the mean venous pressure in life was raised above 8 mm. of mercury evidence of tricuspid valvular incompetence was found at necropsy.

The mode of production of this incompetence and its significance is discussed.

We should like to thank Professor McMichael for his continued help and advice.

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THE MECHANICAL PROPERTIES OF THE LUNGS IN PATIENTS WITH PERIODIC BREATHING

BY

DAVID MENDEL AND MALCOLM B. McILROY

From the Medical Professorial Unit, St. Bartholomew's Hospital and the Institute of Cardiology

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Cheyne (1818) first described periodic breathing in " a case of apoplexy in which the fleshy part of the heart was converted into fat ". In describing the pattern of breathing he wrote: " his breathing was irregular; it would entirely cease for a quarter of a minute, then it would become perceptible, though very low, then by degrees it became heaving and quick, and then it would gradually cease again. This revolution in the state of his breathing occupied about a minute, during which there were about thirty acts of respiration." A similar case was described 36 years later by Stokes (1854) and since then the condition of Cheyne-Stokes breathing has been the subject of numerous papers. Although there has been a tendency to give the name of Cheyne-Stokes breathing to all forms of periodic breathing, it will be seen from the original description that it is more accurate to reserve the term for cases in which there is a definite period of apnœa and the length of the cycle is of the order of one minute.

As a result of the work of Pryor (1951), Gilmore and Kopelman (1954) and Guyton *et al.* (1955), it has been shown that changes in the activity of the respiratory centre and prolongation of the circulation time are important factors in the production of Cheyne-Stokes breathing. Periodic breathing occurs in patients with cerebral or cardiovascular disease and it has been suggested in the past that it is possible to distinguish a central and a peripheral type of periodic breathing. It is generally recognized that in patients with cerebral lesions, the cycle is shorter and apnœa is more likely to occur. Christie and Hayward (1943) suggested that the type of periodic breathing found in patients with left ventricular failure was due to waxing and waning pulmonary congestion. They measured the intra-pleural pressure and tidal volume in anæsthetized cats and rabbits and found that although the intra-pleural pressure swing remained constant the tidal volume underwent cyclic changes. Their findings could only be interpreted as indicating cyclical changes in the mechanical properties of the lung.

This paper reports the results of study of the mechanical properties of the lungs in patients with periodic breathing in which an attempt has been made to assess the part played by waxing and waning pulmonary congestion in the production of periodic breathing in man.

METHODS

The mechanical properties of the lungs were measured from simultaneous records of intra-œsophageal pressure and air flow. The patients, who were all sufficiently ill to make it difficult to obtain their co-operation, were studied sitting or semi-recumbent in bed. Intra-œsophageal pressure was measured either with a water filled tube (Dornhorst and Leathart, 1952) or a long air filled balloon (Mead *et al.*, 1955) connected to an electromanometer. The tidal volume was measured by several different methods, none of which was entirely satisfactory. In most of the patients a spirometer or pneumotachograph was used and in the others a combined thoracic and abdominal pneumograph (Dornhorst and Leathart, 1952) gave a record that could be calibrated in terms of volume. The principal difficulty in the use of a spirometer or pneumotachograph is that the

disturbance produced by breathing through a mouthpiece is often sufficient to abolish periodic breathing. The use of a pneumograph avoids this difficulty but is less accurate and difficult to calibrate.

The compliance of the lungs and the inspiratory resistance were measured, whenever possible, during the cycles of periodic breathing. In half the cases, however, the breathing became regular when the patient breathed through a mouthpiece. In these patients a record of intra-œsophageal pressure alone was obtained during periodic breathing and the mechanical properties of the lungs measured from the tracing taken when the breathing was regular. The length of the cycle of periodic breathing, the length of the period of apnœa, if present, and the respiratory rate were measured in each case. In one patient the oxygen saturation was measured with an ear oximeter.

Results

The results in ten patients with periodic breathing are shown in Table I. All were men and all had evidence of cardiovascular disease. Four had classical Cheyne-Stokes breathing with a period

TABLE I
Results in Ten Patients with Periodic Breathing

Name	Age	Length of complete cycle in seconds	Number of breaths per cycle	Length of apnœa in seconds	Maximum respiratory rate during cycle/min.	Minimum respiratory rate during cycle/min.	Lung compliance l./cm.H_2O	Inspiratory resistance cm.H_2O/l./sec.	Simultaneous tracings	Diagnosis and remarks
A.L.	49	48	13	10	20	—	0·13	2·3	−	Coronary thrombosis Heart failure
W.S.	58	40	21	—	33	28	0·13	1·9	+	Cerebral hæmorrhage Coronary thrombosis Dissecting aneurysm (P.M.)
A.S.	58	58	22	—	29	19	0·048	9·6	−	Coronary thrombosis
		58	14	20	28	—	0·034	11·6	+	Heart failure
G.C.	59	30	7	11	23	—	0·22	2·5	−	Uræmia
C.A.	62	16	15	—	60	50	0·040	6·0	−	Chronic bronchitis Emphysema, hypertension
		17	12	3	60	—				Heart failure
M.J.	66	60	24	—	26	20	0·126	2·6	+	Coronary thrombosis
		56	14	22	26	—	0·084	2·8	−	Heart failure
C.B.	68	60	17	—	18	16	0·14	3·9	−	Malignant hypertension Cerebral thrombosis Heart failure (P.M.)
F.S.	69	40	26	—	30	24	0·053	7·0	+	28.10.54. Hypertension
		38	22	—	30	23	0·049	8·5	+	26.5.55. Heart failure
H.B.	74	65	22	—	28	18	0·061	6·3	+	Coronary thrombosis Heart failure (P.M.)
C.G.	74	60	26	—	28	21	0·108	4·8	−	Coronary thrombosis Heart failure

of apnœa lasting 10–22 seconds and a cycle length of 30–58 seconds. Five had periodic breathing with a cycle length of 38–65 seconds but no period of apnœa, while the other patient had a shorter cycle of 16–17 seconds with an apnœic period of 3 seconds on occasions. Two of the patients with classical Cheyne-Stokes breathing did not always have apnœa, in some cycles there was no apnœa while in others apnœa lasted up to 22 seconds.

It will be seen from Table I that the mechanical properties of the lungs varied considerably from patient to patient, being within normal limits in some and showing a marked reduction in compliance and an increase in respiratory resistance in others. A simultaneous tracing of intra-œsophageal pressure and tidal volume in patient F.S. is shown in Fig. 1. It will be seen that the pressure and volume tracings wax and wane together indicating a periodic variation in the force applied to the lungs, presumably due to periodic changes in the activity of the respiratory centre. This periodic fluctuation in the pressure record was seen in every patient studied and moreover there was no

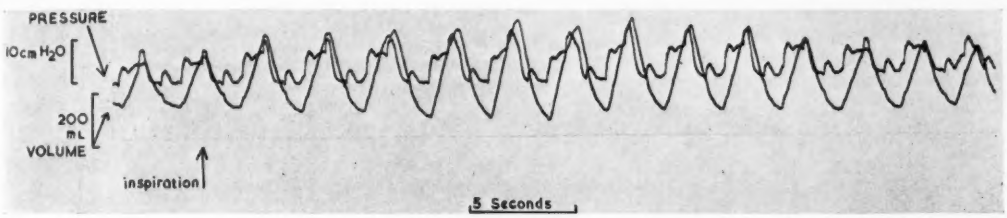

FIG. 1.—Tracing of intra-œsophageal pressure and tidal volume, showing periodic breathing in a patient with left ventricular failure.

consistent variation in the compliance and respiratory resistance measured from breath to breath throughout the cycle in the five patients in whom simultaneous tracings were obtained during periodic breathing.

A tracing of intra-œsophageal pressure in M.J. is shown in Fig. 2. In this patient there was a period of apnœa in some cycles but not in others and it will be seen that the respiratory rate and the pattern of the pressure tracing were essentially the same whether there was a period of apnœa or not. In the patient (C.A.) in whom oxygen saturation was measured, it was found to reach a maximum of 98 per cent during the apnœic period and a minimum of 91 per cent at the time of maximum hyperpnœa. This finding is similar to that previously reported by Klein (1930).

DISCUSSION

If there is a form of periodic breathing due to waxing and waning pulmonary congestion, it should differ from that seen in patients with normal lungs and should not be associated with a period of apnœa, for apnœa must indicate a temporary cessation of activity of the respiratory centre.

We have found no evidence of waxing and waning pulmonary congestion in ten patients with heart disease and periodic breathing, in several of whom there was significant pulmonary congestion and no period of apnœa. In every patient the intra-œsophageal pressure tracings were compatible with cyclical changes in the activity of the respiratory centre and in no case was there evidence that the mechanical properties of the lungs changed from breath to breath throughout the cycle. We have not observed anything resembling the pattern reported by Christie and Hayward (1943) in animals in which the intra-pleural pressure fluctuations remained of constant amplitude while the tidal volume showed periodic breathing. It is, however, impossible to exclude the existence of such a form of periodic breathing.

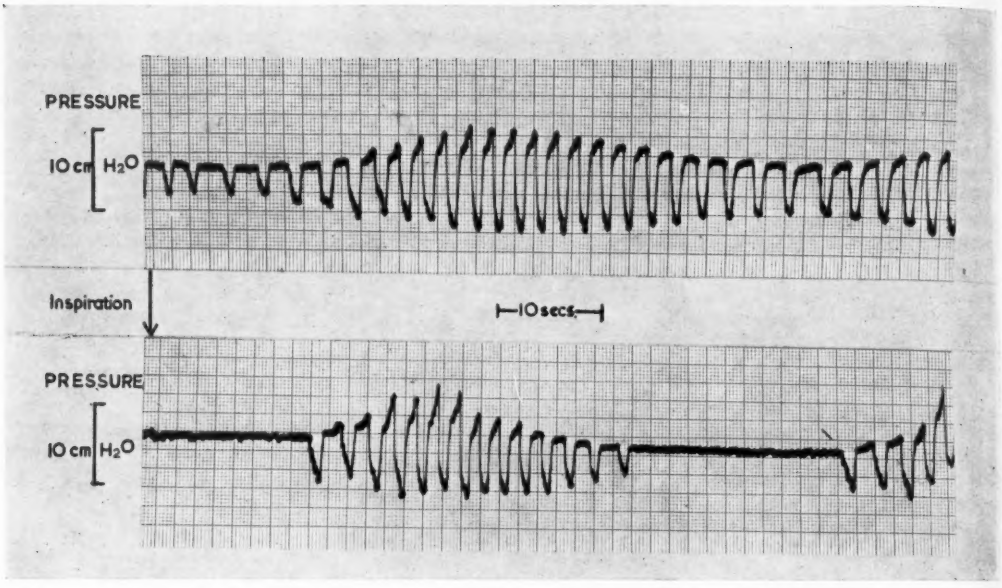

FIG. 2.—Tracings of intra-œsophageal pressure in a patient with periodic breathing. The upper tracing shows no apnœic period, while the lower tracing obtained several minutes later shows apnœa lasting 22 seconds.

SUMMARY

The mechanical properties of the lungs have been measured in ten patients with periodic breathing. The compliance of the lungs and the respiratory resistance varied, being within normal limits in some and grossly abnormal in others.

The intra-œsophageal pressure record in every case showed variations in the force applied to the lungs similar to those in tidal volume and there was no evidence that the mechanical properties of the lungs varied at different phases of the cycle of periodic breathing.

These findings support the conclusion that periodic fluctuations in the activity of the respiratory centre play an important part in the production of periodic breathing and indicate that waxing and waning pulmonary congestion was not a factor in the patients studied.

We wish to thank Dr. G. W. Hayward for his help and encouragement.

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ENDOCARDIAL CUSHION DEFECTS

COMMON ATRIO-VENTRICULAR CANAL AND OSTIUM PRIMUM

BY

MAURICE CAMPBELL AND G. A. K. MISSEN

From the Cardiac Department and the Department of Pathology, Guy's Hospital, and the Institute of Cardiology

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Advances in the surgical treatment of atrial septal defect have made the recognition of the less common varieties of practical importance. There is general agreement on the definition of ostium secundum defects but some confusion about the nomenclature of persistent ostium primum and the common atrio-ventricular (A-V) canal.

When the dorsal and ventral A-V endocardial cushions fail to fuse and to develop normally in fœtal life, the extent of this failure is reflected in the severity of the resulting defect. At one extreme lies the persistent common A-V canal furnished with anterior and posterior valve cusps each common to the two ventricles, the single orifice being continuous above with a persistent ostium primum and below with a high ventricular septal defect. The opposite extreme is simply a persistent ostium primum with, as a rule, a bifid anterior cusp of the mitral valve. Between these two extremes all gradations can occur.

Embryology. During the sixth week of fœtal life the dorsal and ventral endocardial cushions come together by their own growth and fuse to form a common mass, so dividing the A-V canal into separate right and left canals (Patten, 1949). The concave lower edge of the septum primum then joins with the fused endocardial cushions, but union does not become complete before the formation of the ostium secundum. There is some discussion as to whether this fusion is achieved solely by downward growth of the septum primum, or in part also by upward growth of the cushion tissue. The endocardial cushions give rise to the cusps of the mitral and tricuspid valves: they also combine with the inferior ends of the two conus ridges and with further cushion tissue on the crest of the muscular ventricular septum to form the pars membranacea septi, so finally separating the ventricles (Kramer, 1942).

If fusion of the dorsal and ventral cushions fails entirely, the common A-V canal persists, and with it—as integral parts of the extreme defect that we call Grade III—the ostium primum and a high ventricular septal defect, the three deficiencies being continuous. This, with other associated anomalies, is illustrated by our Case 1 (Fig.1), and an intermediate (Grade II) malformation by our Case 2 (Fig. 2). Here the dorsal and ventral cushions have just succeeded in fusing, as shown by the narrow bridge of fibrous valvular tissue attached to the upper surface of the ventricular septum, but their fusion has been insufficient to allow the formation of either the anterior leaflet of the mitral valve or the septal leaflet of the tricuspid valve, so that both valves appear to have been incompetent: no interventricular communication remains, but there is a large persistent ostium primum.

The least severe type of lesion (Grade I) usually consists of a persistent ostium primum and a bifid anterior mitral cusp. Division of the A-V canal occurs, and the tricuspid valve is commonly normal, though occasionally it may be malformed instead of—or even as well as—the mitral valve. As Wakai and Edwards (1956) have suggested, the usual version of this anomaly is evidently the

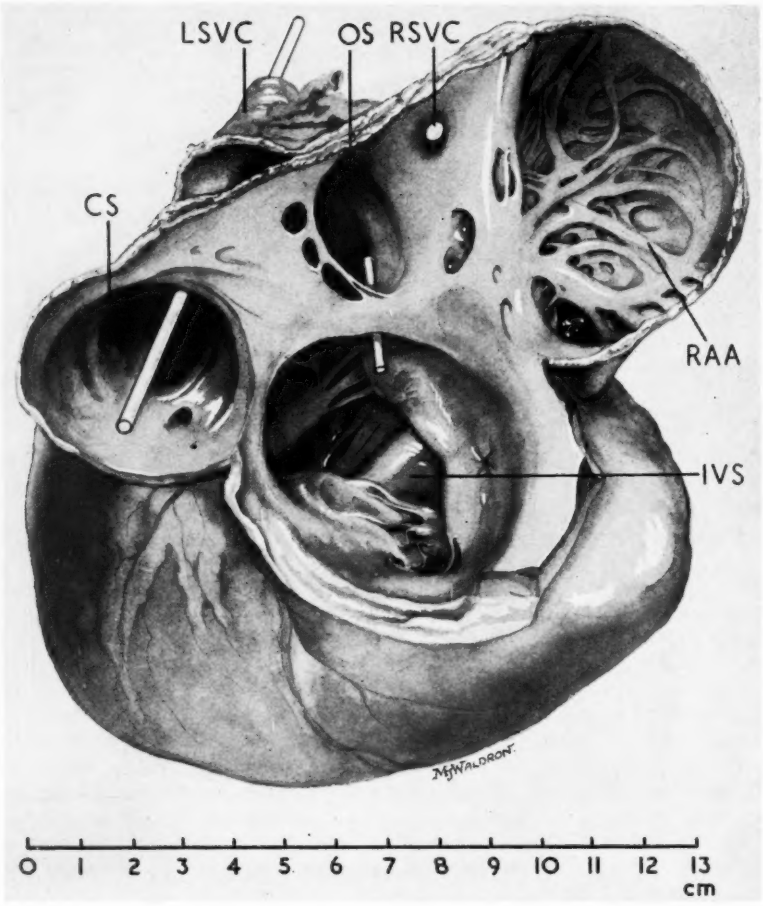


FIG. 1.—Drawing from Case 1. The hypertrophied and dilated R. atrial appendage has been reflected forwards to afford a view into all chambers of the heart from above, behind, and to the right. IVS, upper border of muscular ventricular septum. RSVC, orifice of (small) R. superior vena cava. OS, ostium secundum defect in atrial septum. CS, orifice of enlarged coronary sinus, through which the left SVC drained in the R. atrium.

result of deficient fusion of the dorsal and ventral endocardial cushions *on their left sides only*. Asymmetrical fusion of these cushions clearly took place in our Case 2, in which fusion failed completely *on the right*, but was partially achieved on the left. Ostium primum defects associated with normal A-V valves are occasionally reported, e.g. by Blount *et al.* (1953, Case 3) but are generally regarded as exceptional (Abbott, 1936; Brown, 1950; Edwards *et al.*, 1954; and Wakai and Edwards, 1956).

Nomenclature. Wakai and Edwards have designated this whole group of defects as examples of persistent common A-V canal, modifying the term by the following prefixes: (1) "complete form," which is self-explanatory; (2) " partial form," by which they mean a persistent ostium primum with a bifid anterior mitral valve-cusp; and (3) " transitional varieties " which includes

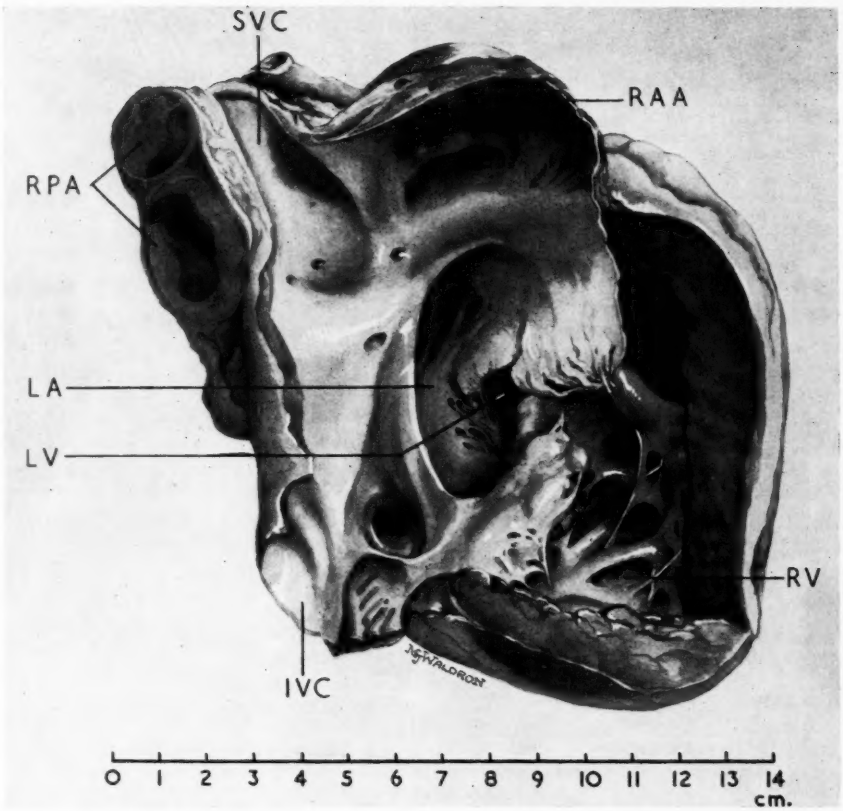


FIG. 2.—Case 2. The hypertrophied R. heart has been laid open to show the failure of fusion of the precursors of the septal cusp of the tricuspid valve, and the ostium primum defect, through which one looks into L. atrium and ventricle. Both primary subdivisions of the R. pulmonary artery (RPA) are almost occluded by thrombus.

hearts showing clefts in both the mitral anterior and the tricuspid septal valve-cusps, and a narrow bridge of valvular tissue immediately above the ventricular septum joining the anterior halves of the bifid cusps with their respective posterior halves: but for this narrow bridge a common A-V valve would be present.

We agree that a collective name for the whole group is needed that will emphasize the embryological relationships, but we cannot accept the nomenclature of Wakai and Edwards, for it is incorrect to describe an ostium primum defect as a common A-V canal, which it is not. Further evidence of the need for an accurate nomenclature, and especially for one employing a less confusing collective term, is supplied by two recent papers from the Mayo Clinic (Wakai *et al.*, 1956; and Cooley and Kirklin, 1956). Both are concerned with series of cases of " persistent common A-V canal ": except in two cases, however, the definitive prefixes of Wakai and Edwards are omitted, to the bewilderment of the reader, who cannot be certain whether an individual patient discussed had, in fact, a single common A-V canal or a less severe malformation.

A solution lies in the term " endocardial cushion defect " recently used by Watkins and Gross

(1955) as a synonym for the ostium primum defect. The system of nomenclature that we prefer is shown below, together with the terms of Wakai and Edwards.

Proposed classification and names	Names proposed by Wakai and Edwards (1956)
Endocardial cushion defect, Grade I Persistent ostium primum	Persistent common A-V canal, partial form
Endocardial cushion defect, Grade II	,, ,, ,, ,, transitional varieties
Endocardial cushion defect, Grade III Persistent common A-V canal	,, ,, ,, ,, complete form

We have no wish to displace such well-established terms as persistent ostium primum and persistent common A-V canal, provided that the latter is used only when truly applicable, but there is no accepted name for the Grade II defects which therefore lead to confusion. Persistent common A-V canal is clearer and more easily understood than the alternative terms of ostium atrioventriculare commune or atrio-ventricularis communis.

We think the term endocardial cushion defects has the following advantages. First, it emphasizes the kinship of a range of embryologically related malformations by directing attention to a developmental failure that, in varying degrees, is common to all the grades of defect within the group. Secondly, it is accurate as a collective term for the whole group, neither overstating nor understating the severity of the anomaly in any individual case: with the addition of an appropriate suffix it can be used with equal propriety to indicate all the principal degrees of maldevelopment. Finally, it provides a satisfactory name for the intermediate forms exemplified by our Case 2 and in three cases of Wakai and Edwards.

Case 1. Endocardial cushion defect, Grade III (persistent common atrio-ventricular canal). Second (ostium secundum) atrial septal defect. Stenosis of bicuspid pulmonary valve. Rudimentary accessory tricuspid orifice. Persistent L. superior vena cava.

The mother of this girl said that her lips were first cyanosed at the age of five months, and breathlessness was noticed at eighteen months when she began to walk. At the age of six when first seen by us, she had central cyanosis and was somewhat disabled though she could walk half a mile. She did not squat. A systolic murmur and thrill were found widely over the left side, and below the pulmonary area a diastolic murmur was heard at some visits but not regularly. The heart was large (c.t.r. 60%, Fig. 3A) and this was thought to be due mainly to the right atrium and right ventricle but partly to the left ventricle as well. The lung fields looked dense but there was no pulsation beyond the hila and the pulmonary flow did not seem much increased. The electrocardiogram showed a large broad P wave in several leads suggesting strain on both atria, but no ventricular preponderance; the primary *r* wave was so minute that one could hardly speak of a secondary *R* wave (Fig. 4A).

When she was 12 she was no more disabled and her heart was no larger but she was more cyanosed and now had right ventricular preponderance (Fig. 4B). She was admitted for catheterization, which proved a left-to-right shunt into the right atrium (S.V.C. 43%, R.A. 71%) presumably through an atrial septal defect, and revealed a left-sided S.V.C. that drained into the right atrium through the coronary sinus. The pressure in the atria was almost the same (R.A., 11/6; L.A., 10/6). The oxygen saturation on the left side was not much higher than on the right (F.A. 79%; L.A. 75%; R.A. 71%) so that it seemed as if there was also a right-to-left shunt at atrial level, though the pressure in the right ventricle (51/6) was much lower than in the left (118/11). The systemic flow was 2·4 litres and the pulmonary flow 4·1 litres a minute with an overall left-to-right shunt of 1·7 litres, which explained why the pulmonary flow had not seemed very large on radioscopy. Two years later, when she was 14, she looked a healthy girl and could walk four miles, but we were shocked by the increased size of her heart (c.t.r. 70% (Fig. 3B)) especially to the right.

She was, therefore, admitted for reinvestigation to decide if surgical treatment was possible. While waiting she developed supra-ventricular paroxysmal tachycardia at a rate of 164 a minute: it could not be stopped and she developed congestive heart failure and died three days later. Permission was granted for examination of the heart only.

Necropsy. The pericardium was normal. Inspection of the heart *in situ* showed gross enlargement, especially of the right side (Fig. 5), and a persistent left S.V.C. The heart weighed 425 g. (range for normal

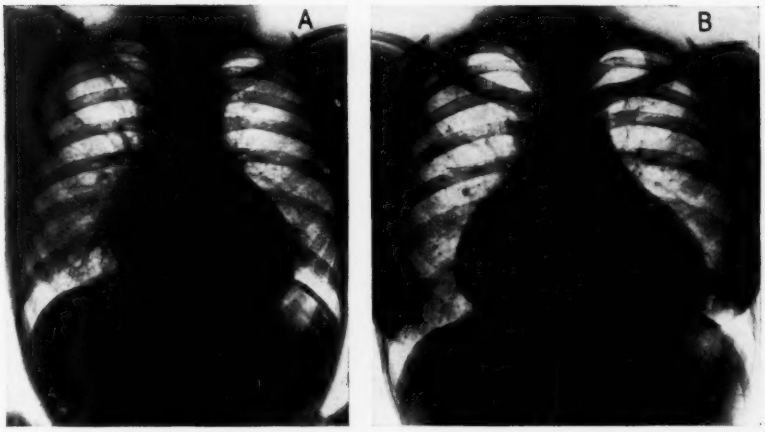


FIG. 3.—Teleradiograms of the heart, showing progressive enlargement, especially of the right side. (A) In 1948 when she was 6 and again in 1954 the cardiothoracic ratio was 60 per cent. (B) In 1956 shortly before her death it was 70 per cent. Case 1 with a Grade III endocardial cushion defect.

women of the same stature, 263±30 g.; Zeek, 1942). Its maximum transverse diameter across the bases of the ventricles was 122 mm., 13 mm. more than the distance from apex to base of ventricles.

The R. atrium was hypertrophied and enormously dilated: the I.V.C. and a small R. S.V.C. entered it in normal fashion, and the L. S.V.C. via the coronary sinus, which was, therefore, greatly enlarged, its atrial orifice measuring 35×30 mm. (Fig. 1). The atria communicated by way of two large septal defects. Above was an ostium secundum defect bounded posteriorly by a fenestrated remnant of the septum primum (Fig. 1 and 7): including the fenestrae, it measured 32 mm. vertically by 28 mm. sagittally (the heart being considered for convenience of description as vertical with the apex pointing downwards). Separated from this defect by a narrow band of septal muscle, only 10×3 mm. in cross-section, was a large ostium primum defect with a falciform upper border. This was continuous through a common A-V canal with a high ventricular septal defect, bounded below by the upper edge of the muscular ventricular septum (Fig. 1 and 7), which was concave anterio-posteriorly, though convex from side to side. The entire resultant defect measured 43 mm. sagittally ×35 mm. vertically.

The common A-V canal (Fig. 1 and 6) measured 50 mm. across its greatest diameter; its valve consisted of one large anterior and one large posterior cusp, each common to the two ventricles, with a third smaller cusp confined to the L. ventricle.

The wide *posterior cusp* was attached by chordæ tendineæ to papillary muscles in both ventricles and to the right side of the septum. Its anterior edge was opaque, thickened, and rolled, while the cusp itself was widely and closely bound down to the upper edge of the muscular ventricular septum by fibrous tissue, which must have prevented it from floating into apposition during ventricular systole, and so made the valve incompetent. The wide *anterior cusp* (Fig. 6) extended, in addition, around the lateral aspect of the R. ventricle to meet the common posterior cusp. The former was about 2 mm. thick and was anchored by chordæ to the anterior papillary muscles of both ventricles and also to accessory papillary muscles of the right, but unlike the posterior cusp was not attached to the ventricular septum. A group of short chordæ arising from the anterior papillary muscle of the R. ventricle was attached to the under surface of the common anterior cusp away from its free margin. At this point the cusp was pierced by a small puckered perforation (Fig. 1), evidently a rudimentary accessory tricuspid orifice, the result of incomplete fusion of the ventral and R. lateral A-V endocardial cushions at this point (see Wimsatt and Lewis, 1948). The *third cusp* was confined to the L. ventricle and represented the posterior cusp of the mitral valve. It was of normal structure, and was attached by chordæ to the anterior and posterior papillary muscles, principally to the latter. The ventricular septum was much hypertrophied, its maximum thickness being about 25 mm. The pars membranacea was absent.

The R. ventricular wall was greatly hypertrophied, being 12 mm. thick in the outflow pathway 20 mm. below the pulmonary valve (normal range 2–3 mm.; Saphir, 1951). The infundibulum was otherwise normal, but there was moderate stenosis of the pulmonary valve, which was bicuspid owing to fusion of its posterior and R. anterior cusps. Both cusps were abnormally thick and opaque with wrinkled surfaces,

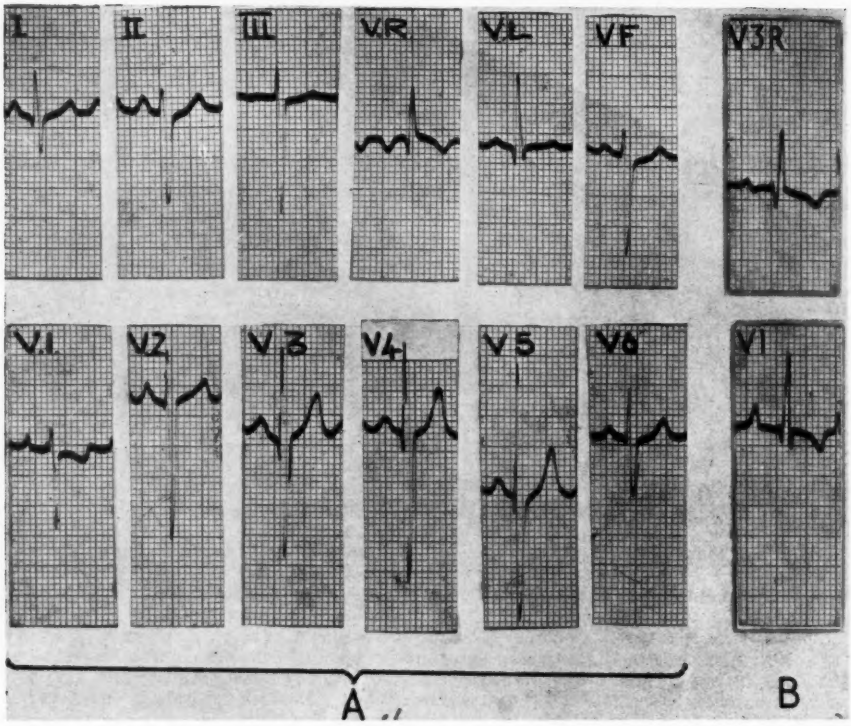


FIG. 4.—Electrocardiograms from Case 1. (A) When she was 7, showing left axis deviation and perhaps some left ventricular preponderance. The large broad P waves in lead II and some other leads suggest some strain on both atria. Standardization normal above, but 1 MV=0·5 cm. in leads V1–V6. The QRS complex is only 0·08 sec. wide in V1 and a primary R wave can only just be seen, though it is rather larger in V3R.
(B) When she was 14, showing right ventricular preponderance. This had been the same for three years, but seven years before there was no right ventricular preponderance (Fig. 2A).

and the fusiform valvular orifice measured 11×6 mm. The internal diameter of the pulmonary trunk just above its valve was 13·5 mm., and that of the aorta at a corresponding level, 11 mm.

The pulmonary veins drained normally into the L. atrium, which showed moderate hypertrophy but little dilatation. The L. ventricle was hypertrophied (14 mm.). The aortic valve cusps were thickened and reddened but there was no fusion: both aortic and pulmonary valves appeared competent. The coronary arteries were small, thin-walled, and patent throughout. The myocardium appeared normal.

Case 2. Endocardial cushion defect, Grade II. Aortic hypoplasia. Massive thrombosis of arteriosclerotic pulmonary trunk and arteries. Pulmonary infarction. Broncho-pulmonary mycotic infection (?Aspergillus).

This woman, aged 38 when she died, knew she had a murmur when she was 7, but had no symptoms. At 19 she became a nurse at Guy's Hospital although her heart murmur was noted. She completed her training without difficulty, but was unduly tired after a period of heavy work. In 1944, when she was a Sister and aged 27, she became dyspnœic on hills and cyanotic in cold weather: unfortunately, no X-ray or cardiographic examination was made at this time or earlier. In 1946 she married and went to India and became aware of some disability. After hysterectomy for recurrent menorrhagia, she began to notice

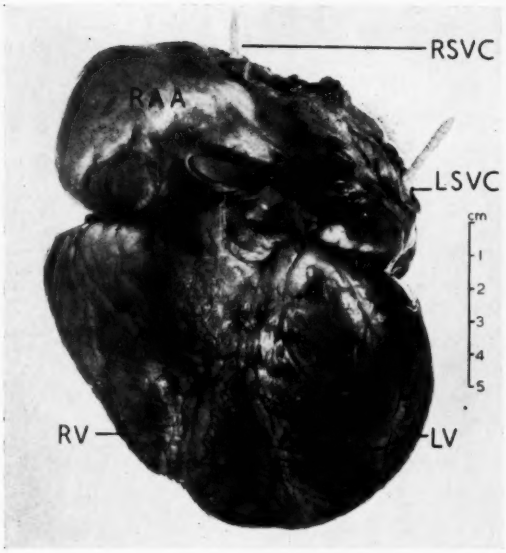


FIG. 5.—Case 1. Anterior aspect of the heart, showing great enlargement of R. atrial appendage and R. ventricle. The L. ventricle is less enlarged. The markers indicate the sites of entry of the two superior venæ cavæ.

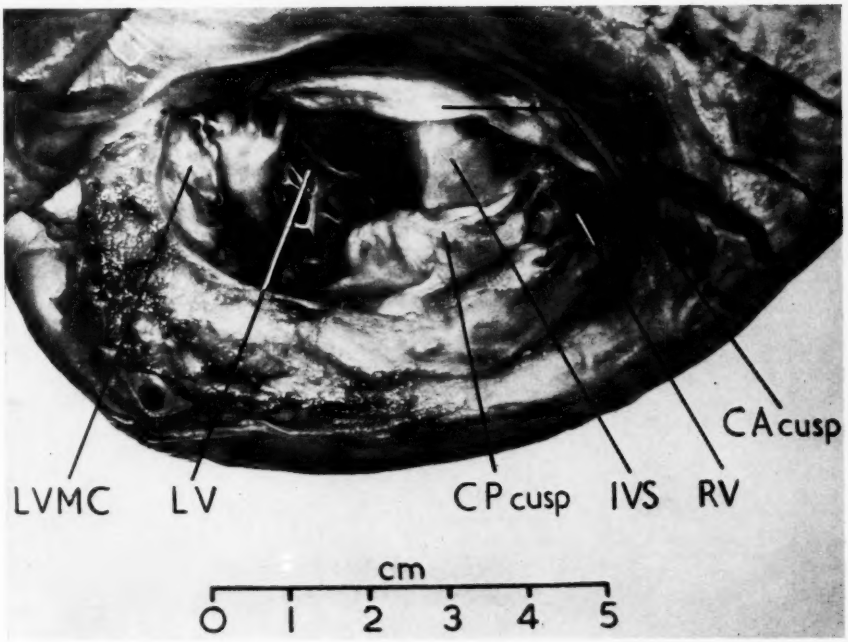


FIG. 6.—Case 1. The common atrio-ventricular canal from above after reflection of the atria forwards. CA cusp and CP cusp, common anterior and posterior cusps. IVS, ventricular septum. LVMC corresponds to posterior cusp of mitral valve.

hills more and, in 1950, had to give up cycling. It was difficult to say when her cyanosis had become permanent, probably about 1948.

In 1953 when she was 35 years old and was becoming severely disabled, she was examined. She had classical signs of atrial septal defect and pulmonary hypertension, a large heart (c.t.r. 64%), a tapping apex beat, a systolic murmur and thrill well heard towards the apex, and a loud second sound in the pulmonary area. The blood pressure was 120/85. The cardiogram showed gross right ventricular preponder-

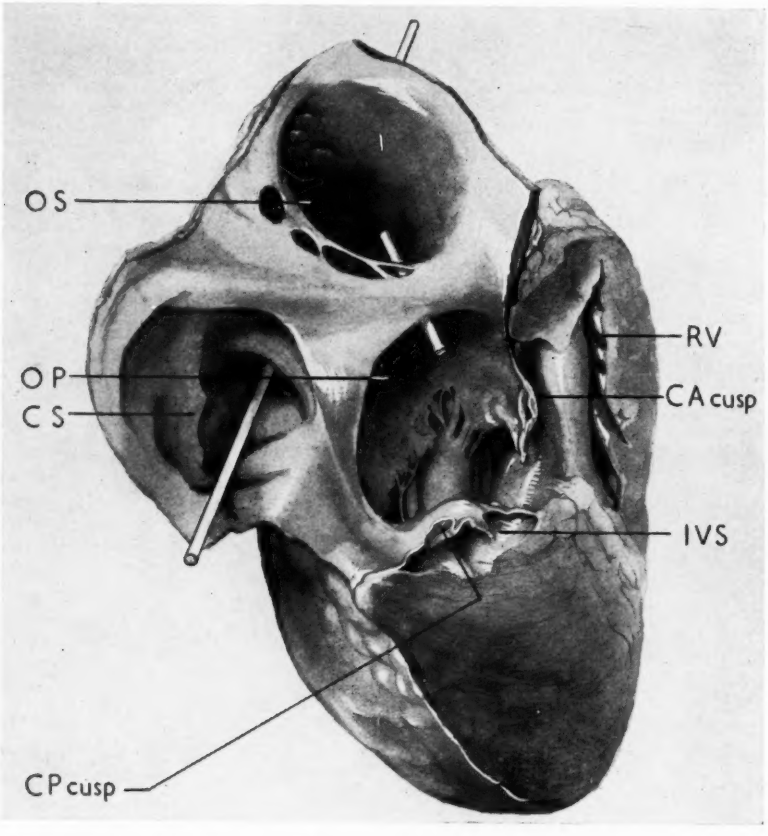


FIG. 7.—Drawing from Case 1. The greater part of the R. atrium and ventricle have been removed to demonstrate the inter-ventricular communication beneath the cusps of the A-V valve. OS, ostium secundum defect. OP, ostium primum defect. CS, orifice of coronary sinus (rod in left SVC). CP cusp and CA cusp, divided common posterior and anterior cusps. IVS, upper edge of muscular ventricular septum. RV, hypertrophied wall of R. ventricular outflow pathway.

ance with S–T depression and/or T inversion in leads II, III, and V1 to V4, and a P–R interval of 0·23 sec. There was moderate central cyanosis, although radioscopy still showed increased pulsation in the pulmonary branches, which were enormous.

At *catheterization* a few months later the pressure was the same in both atria (5/–1). There was a right-to-left shunt (arterial O_2, 76%) and a smaller left-to-right shunt; the pressure in the pulmonary artery was 140/62 mm., slightly above the systemic pressure; and the pulmonary arteriolar resistance was greatly

increased (32 units). The clinical diagnosis was bi-directional shunts through an atrial septal defect with pulmonary hypertension.

She became much worse during the next year when she was thought to have had a pulmonary embolism though, in retrospect, this was almost certainly pulmonary thrombosis. She began to get cardiac asthma and had to confine her activity to the lightest housework. She generally had two days in bed each week and needed a low salt diet with digitalis and mersalyl. In 1956, three years after her catheterization, she became worse rather suddenly with attacks of unconsciousness on the slightest exertion, and died after a few days in hospital. A necropsy was performed by Dr. C. H. R. Knowles, to whom we are indebted for his report, and for the heart and lungs.

Post-mortem Findings. The heart (410 g.) was enlarged (Fig. 8A). The two venæ cavæ and the coronary sinus entered the R. atrium normally. The foramen ovale was patent to the probe, but of normal valvular structure. Much of the atrial septum was absent as there was a large ostium primum defect measuring 49×32 mm. (Fig. 2). It was bounded below by the upper border of the muscular ventricular septum, to which malformed and thickened A-V cusps were firmly bound down (Fig. 9). The pars membranacea septi was absent. The R. atrium was moderately hypertrophied and dilated.

Both the mitral and tricuspid valves had, in effect, three cusps. The rather small posterior mitral cusp was anchored by chordæ directly to the ventricular wall; otherwise it was normal. Owing to maldevelopment and incomplete fusion of the ventral and dorsal endocardial cushions, the anterior mitral cusp was represented by two short, thick, fibrous cusp-like structures, one anterior and one posterior, which just met and became continuous on the upper surface of the ventricular septum, to which both were firmly and extensively bound down (Fig. 9). Clearly this valve had been incompetent: this had not been recognized in life though the systolic murmur and thrill had been specially noted in the mitral area. The bases of both these cusp-like structures were continuous with the anterior and posterior components respectively of the septal cusp of the tricuspid valve. These had remained completely unfused and, though thickened and malformed, were more supple than their mitral counterparts. The anterior component was anchored to the anterior papillary muscle of the R. ventricle, and the posterior by short chordæ to the right side of the ventricular septum. The anterior and inferior cusps of the tricuspid were normal, except that the latter was fused with the posterior component of the septal cusp: if this had not been so, the tricuspid valve would have had four cusps. It too had almost certainly been incompetent from birth.

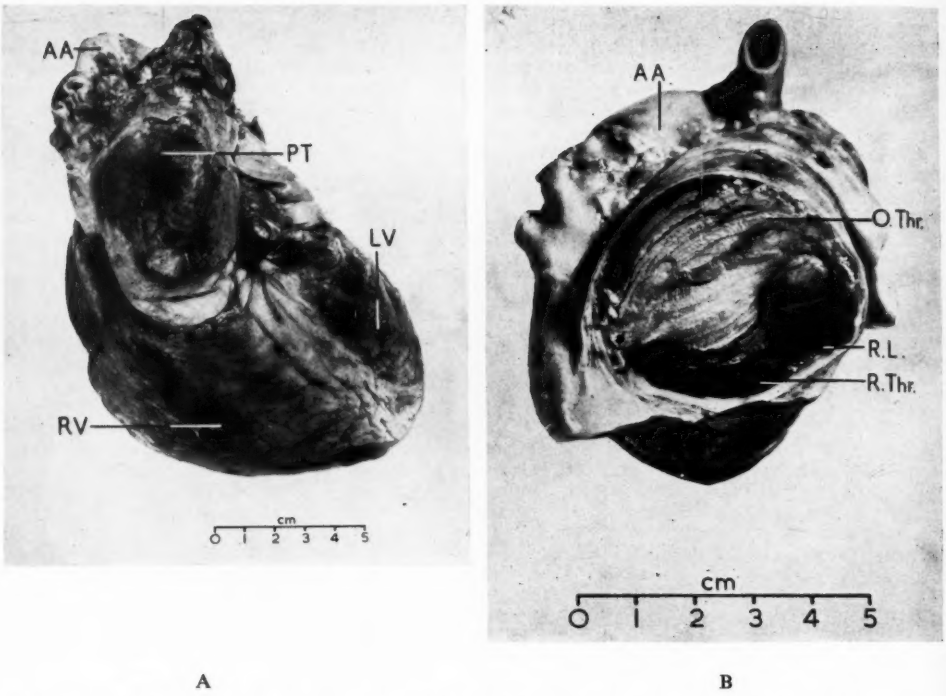
The R. ventricle was dilated and greatly hypertrophied (Fig. 2), the wall of its outflow pathway being 14 mm. thick at a level 20 mm. below the pulmonary valve (normal 2–3 mm.). There was no pulmonary stenosis, either valvular or infundibular: the valve-cusps were normal and the ring of normal diameter (27 mm.). Beginning just above the valve-ring there was massive thrombosis of the pulmonary trunk, extending along both arteries and their main subdivisions into the lungs. Transverse cuts across these vessels revealed that the process had been one of gradual accretion over a long period. Furthest from the slit-like lumina that remained the thrombus was hard, yellow, and laminated, with calcification in the oldest strata, whereas adjacent to the lumina it was dark red thrombus of recent origin (Fig. 8B). All these arteries showed a great increase in external diameter, but the lumina remaining were small by comparison.

Artery	External diameter	Residual lumen (Greatest cross-section)
Pulmonary trunk	48×42 mm.	6×35 mm.
R. pulmonary artery ..	44×40 mm.	7×15 mm.
L. pulmonary artery ..	32×28 mm.	5×13 mm.

Indeed the branch to the R. upper lobe became totally occluded by thrombus before it entered the lung, while the main artery of the R. lower lobe had only just entered before it also became occluded: in both cases occlusion had only become complete terminally.

The four pulmonary veins opened normally into a L. atrium that was moderately hypertrophied and dilated, as was the L. ventricle. The aortic valve-cusps were normal, but the valve-ring was only 15 mm. (normal 24 mm.) in diameter. Immediately above their valves the walls of pulmonary trunk and aorta were of the same thickness, while the pulmonary trunk soon became dilated (Fig. 8B). The coronary arteries were normal throughout, showing none of the severe hypoplasia found in the aorta, whose descending arch was only 9 mm. in internal diameter. No ductus arteriosus was found.

Both pleural sacs were traversed by old fibrous adhesions, especially over the medial segment of the R. middle lobe: this showed severe shrinkage and fibrosis of long standing, possibly the end-result of past infarction. At the apex of the R. upper lobe was a recent red infarct with overlying fibrinous pleurisy. The cut surfaces of the lungs revealed that the massive thrombosis extended into all the major branches of the R. pulmonary artery and also those of the L. upper lobe, while throughout both lungs there was atheromatous thickening of the walls of arteries of 3–5 mm. in diameter. In the smallest arteries too,



A B

FIG. 8.—Case 2. (A) An antero-superior view of the heart, showing the great size of the R. ventricle and the (thrombosed) pulmonary trunk (PT). The hypoplastic aortic arch (AA) is also seen.
(B.) Transverse section of the pulmonary trunk, showing the extreme narrowing of its lumen by laminated thrombus. The hypoplastic aortic arch (AA) is also shown. (Chance artefactual kinking of the descending arch has brought its divided end into view, though out of focus). O.Thr., old thrombus. R.Thr., recent thrombus. R.L., residual lumen.

thickening of the walls could be seen with the lens. The R. bronchial artery was slightly enlarged. The parenchyma of both lungs had a brown tinge. In the apical segment of the L. upper lobe was a collapsed sub-pleural cavity about 15×10×7 mm. Nearby in the lung parenchyma were several firm rounded nodules, yellow in the centre, grey at the periphery, and up to 5 mm. in diameter.

The only other noteworthy finding was a congenital shortening or failure of fixation of the colon, as a result of which it possessed no splenic flexure.

Histological Findings in the Lungs. Sections from both upper and both lower lobes were examined. With the exception of a few localized lesions, which will be described, the changes were broadly similar throughout. In describing the various orders of branches of the pulmonary arterial tree, the nomenclature of Brenner (1935) is used.

The elastic arteries collectively showed the following changes: (*a*) complete or almost complete occlusion by organized or organizing thrombus, or eccentric narrowing from the same cause (Fig. 10A and B); (*b*) a gradation of changes ranging from a moderate degree of fibro-elastic sub-intimal thickening, with or without collections of foamy macrophages in its deeper part, through a more severe degree of the same change with narrowing of the lumen, to severe atheroma with patchy medial atrophy; (*c*) a moderate degree of medionecrosis, seen in elastic arteries of the L. lung only, and characterized by interstitial deposition in the media of amorphous basophilic material which stained metachromatically with toluidine blue; and (*d*) early medial calcification, seen in a single artery only.

The muscular arteries showed the following abnormalities: first, complete occlusion or else narrowing of the lumen—sometimes eccentric—by organized or organizing thrombus (Fig. 10D); secondly, sub-intimal fibrosis, sometimes severe (Fig. 10C); and finally medial hypertrophy shown by thickening and

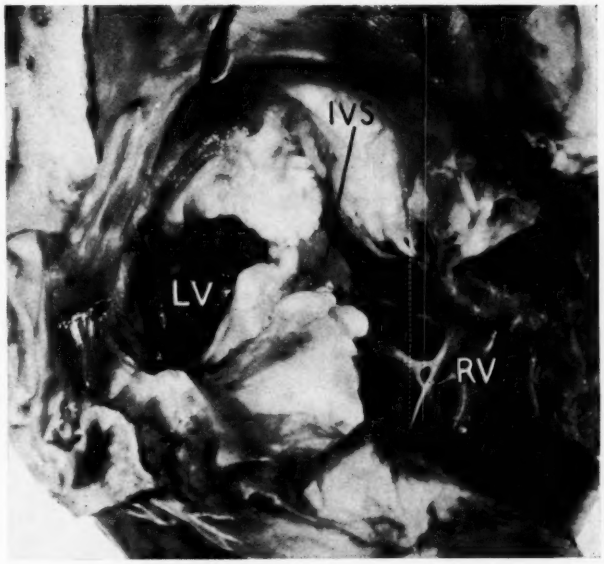


FIG. 9.—Case 2. The atrio-ventricular valves from above, behind, and to the right, after incision of the R. ventricle with division of the anterior tricuspid leaflet. The deformed precursors of the anterior mitral cusp are seen to have fused only at the mid-point of the ventricular septum (IVS). The precursors of the septal tricuspid leaflet have failed to fuse.

reduplication of the internal elastic lamina (Fig. 10C). In one instance as many as six laminæ could be counted.

The condition of those vessels between capillary size and 100μ in diameter, that is, the group including both *arterioles* and *venules*—which may be impossible to distinguish—was variable: some showed little change, whereas others were severely altered. Sub-intimal fibrosis leading to great reduction in lumen was common (Fig. 10F), as was thickening of the elastica with or without reduplication (Fig. 10E), while a few vessels showed complete fibrous occlusion. The appearance of a distinct media bounded by two elastic laminæ, as reported by Heath and Whitaker (1955), was rarely seen. While it is clearly begging the question to postulate that the vessels showing these changes are arterioles, this seems a reasonable working hypothesis.

The lung parenchyma showed moderate patchy emphysema throughout, and several circumscribed foci of old sub-pleural fibrosis with overlying fibrous adhesions, possibly the remains of past infarcts. Recent infarction at the R. apex was confirmed, and found to be complicated by early suppuration.

The abnormal zone of lung at the L. apex was one of old collapse with fibrosis and bronchiolectasis. Several dilated bronchioles contained radiate masses of branching, septate, fungal mycelium surrounded by pus, while at least one such mass lay within a granuloma in the lung parenchyma, made up of macrophages, plasma cells, lymphocytes, and giant cells. The mean diameter of the mycelium was 3·7μ. No fruiting-heads of the fungus were seen in any section, and, as only formalin-fixed tissue was available, it was impossible to identify it by culture. The organism was very probably *Aspergillus fumigatus*, which grows well in pulmonary infarcts (Hinson *et al.*, 1952; Riddell, 1952 and 1956).

Comment. This patient had at first a large left-to-right shunt, and a large pulmonary blood flow, and later consequent pulmonary hypertension, to which all the vascular changes found can be related. The great size of the pulmonary arteries mirrors the initially high flow. Pulmonary hypertension leads to compensatory medial hypertrophy of muscular arteries, and to thickening and duplication of the elastica of arterioles. Atherosclerosis of the main trunks and large elastic arteries is a familiar concomitant of long-standing pulmonary hypertension, though their precise relationship is uncertain. Slowing of the blood flow in such arteries is liable to lead to mural thrombosis, with subsequent spread both distally and proximally; and, as the thrombus forms, small fragments may be broken off it and carried distally as emboli,

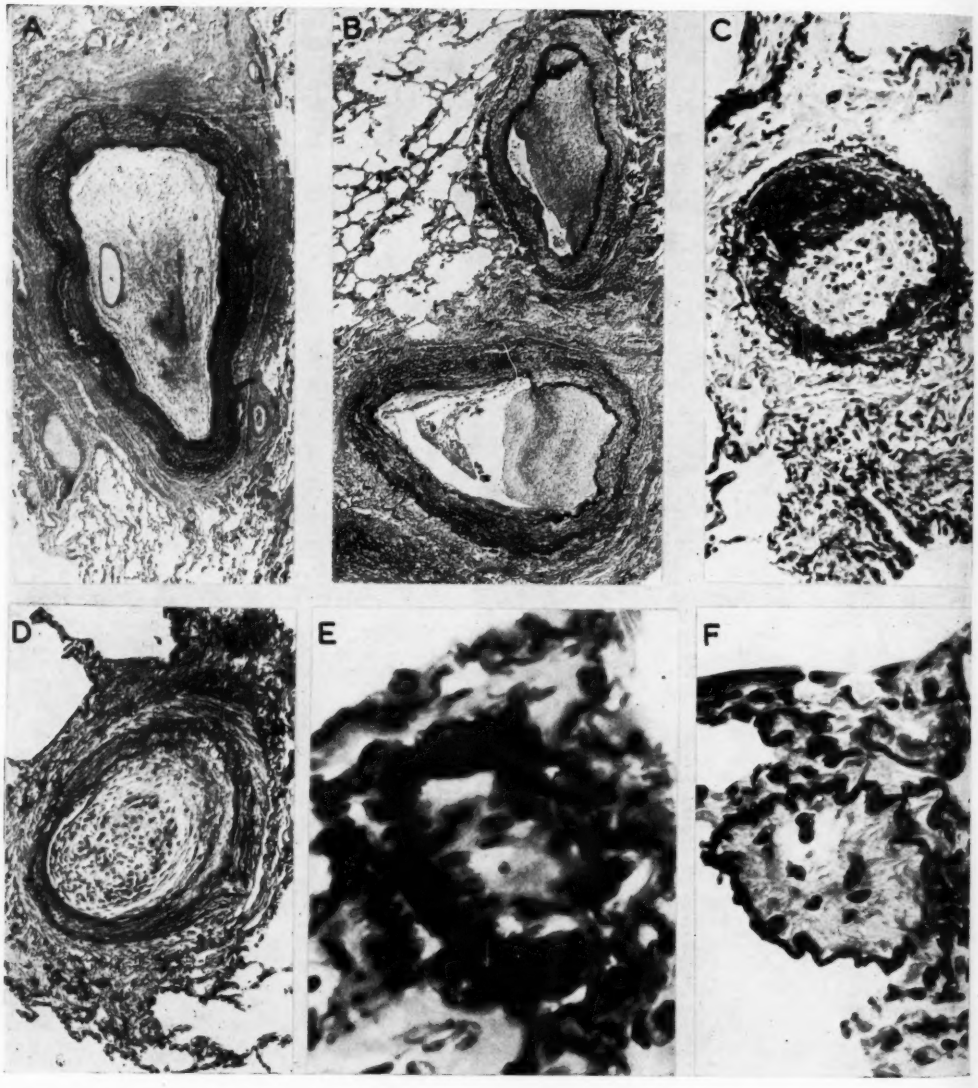


FIG. 10.—Case 2. Photomicrographs of pulmonary vessels. All sections are stained by the Weigert van Gieson method, elastic tissue appearing black. (A) An elastic artery almost completely occluded by organized thrombus. Several recanalizing channels of capillary size are seen, and one larger one. ×19.
(B) Two elastic arteries (1·5 and 1·9 mm.) eccentrically narrowed by organized mural thrombus. ×19.
(C) A muscular artery (170μ), showing medial hypertrophy with thickening and reduplication of the internal elastic lamina. The lumen is almost obliterated by lightly-stained collagen. ×182.
(D) A muscular artery (400μ) blocked by organized thrombus, through which pass a few recanalizing channels of capillary size. ×96.
(E) A (presumed) pulmonary arteriole (50μ). The elastica shows not only hypertrophic thickening, but also reduplication. In parts of the circumference there is a suggestion of a medial coat. Except for a few fine channels, the lumen is obliterated by collagen. ×785.
(F) Another (presumed) arteriole (75μ). The elastica is thickened and there is eccentric sub-intimal fibrosis with reduction of the lumen. ×455.

impacting in vessels of various calibres and becoming organized. The degree of fibrous stenosis ultimately remaining at these sites depends upon the success or otherwise of recanalization. Harrison (1948) demonstrated a strong tendency to recanalization after experimental pulmonary embolism had been produced in rabbits by injecting human fibrin.

The work of Gibbon *et al.* (1932) is relevant to this patient's long survival despite much obstruction. In experiments on cats they showed that gradual occlusion of up to 60 per cent of the cross-sectional area of the pulmonary trunk was without significant effect on the systemic arterial or venous pressures; obstruction of from 60 to 85 per cent led to a rise in venous pressure and a fall in cardiac output and in blood pressure; and only when more than 85 per cent was occluded did death result. In Case 2 the mural thrombus in the main trunk and arteries grew progressively by accretion until it obstructed them so severely that death ensued, but the occlusion took place very gradually in arteries that were already much dilated: these two conditions would clearly favour prolonged survival.

It is interesting to compare these pulmonary vascular changes with those recorded in patent ductus arteriosus by Heath and Whitaker (1955), who found a close relationship between the histological changes in the vessels and the pulmonary arterial pressure. The changes found in two of their cases with a high pressure bore a close resemblance to those in our Case 2, except that they encountered no thrombosis of major arteries, while in our Case 2, whose pulmonary pressure had been 140/62 mm. three years before, a media was rarely seen in the supposed arterioles.

Severe pulmonary hypertension is now regarded as a contra-indication to operative treatment of endocardial cushion defects (Watkins and Gross, 1955; Cooley and Kirklin, 1956).

Discussion

An early report of endocardial cushion defect is that of Peacock (1846–48). His description of the heart from a girl of 10 suggests that she had a persistent ostium primum, a bifid anterior mitral cusp, and an incomplete pars membranacea septi which bulged aneurysmally to the right.

Rokitansky (1875) gave an anatomical description of seven hearts that he considered showed defects of the septum primum. One appears to be an example of the type of high atrial septal defect associated with anomalous pulmonary venous drainage (Trounce, 1953; Hudson, 1955; and Ross, 1956), now called the sinus venosus type. The remaining six all had ostium primum defects and an anterior cusp of the mitral valve that was bifid in all and completely cleft in four: the two components of this cusp were, in each case, fused with the adjacent leaflets of the tricuspid valve above the ventricular septum, but no other malformation of the tricuspid was mentioned. A high ventricular septal defect complicated two cases.

Keith (1909) records having seen 14 examples of the Grade III lesion: they are not described in detail but the essential anatomy is admirably demonstrated by two sketches, which incidentally show also a bicuspid pulmonary valve and what appears to be an ostium secundum defect, as in our Case 1. In Keith's experience the Grade III lesion was usually associated with other defects, such as complete transposition of the great trunks or pulmonary stenosis; death usually occurred in childhood and he had not seen this anomaly in the heart of an adult. Good accounts of single cases are given by Robson (1931), Robinson (1941), and Moragues (1943).

Association with Mongolism. Gunn and Dieckmann (1927) described the hearts of two mongols, aged 4 and 12 months respectively, both with a typical Grade III defect. The frequent association of Grade III and Grade I lesions with mongolism has been stressed by Abbott (1936) and others. Brown (1950) says that half of the 40 reported Grade III cases have been in mongols, and 3 of the 6 assorted cases of Rogers and Edwards (1948) were mongols. The Grade III defect is certainly more common among mongols than among other children but only a seventh of the mongols with congenital heart disease have it, the other defects being of very varied types (Evans, 1950).

The Presence of Cyanosis. Taussig (1947) discusses the clinical and hæmodynamic aspects of the Grade III lesion, and states that, as a rule, the shunt is from left-to-right and there is no cyanosis. In general, the condition is said to be acyanotic and liable to be mistaken for an atrial or ventricular septal defect, but some patients have slight or moderate cyanosis from an early age. This is said to be due generally to additional lesions, particularly pulmonary stenosis (Métianu *et al.*, 1954), but must also be influenced by the size of the defect. In our Case 1 it seemed as if

blood from the enormous right atrium must have passed direct into the left ventricle, and that this was probably one source of her right-to-left shunt.

Prognosis. The prognosis is bad and many patients die in the first two years. The heart is of normal size at birth and Taussig (1947) says it increases slowly; it may, however, increase quickly and become very large, this depending on the size of the defects.

Rogers and Edwards (1948), reporting 6 cases of endocardial cushion defect (4 of Grade III and 2 of Grade I), analyzed the clinical features of these and 50 reported cases that they regarded as acceptable. Their conclusions are based on a series that included both Grade III and Grade I defects. More than half died before one year while only 5 survived beyond the age of 30, the median age at death being 10 months. Bacterial endocarditis occurred in 3 cases only.

Wakai and Edwards (1956) refer to three children who were very similar to our Case 2; both the mitral anterior and the tricuspid septal leaflets were bifid in each case, and there was the narrow bridge of valvular tissue that has been described. In two, both valves were thought to be severely incompetent. Their ages at death were 17 days, 6 weeks, and $3\frac{1}{2}$ years. The mean survival time of 15 months is intermediate between that of 5 patients with Grade I defects (14 years, with a range of 5 months—37 years) and 14 with Grade III defects (about 6 months, if one young infant of unknown age be excluded, all having died before the age of 16 months). However, reference is made to a patient who died elsewhere with a Grade III lesion at the age of 22 years.

Condition of the Mitral Valve. Persistent ostium primum is said by Abbott (1936) always to be associated with cleavage and insufficiency of the anterior mitral cusp. She considers that the heart with a Grade III lesion, including a large septal defect, functions as a biloculate organ, and therefore gives to it the confusing name of " incomplete double heart ": 14 hearts are so classified in her analysis of 1000 cases and in 10 of these it was regarded as the primary lesion. These ten all died before the age of 5 with a mean of 1·5 years. It is hard to tell how many of the cases with " Defects (of) auricular septum below " (half with this as the main defect) should be classed as examples of endocardial cushion defects: Rogers and Edwards (1948) put the figure at 13. In their own two cases of Grade I defect the mitral valve was considered incompetent, while in at least 3 of their Grade III cases tethering of the common posterior cusp to the ventricular septum would have rendered the common A-V valve incompetent also. Such incompetence is of importance both in diagnosis and in surgical treatment. Edwards *et al.* (1954) include among the clinical features of the Grade III lesion the usual presence of a systolic murmur over the mid-præcordium and apex and the radiological finding of equal enlargement of the two ventricles, but these may occur with a Grade I lesion. Such diagnostic clues are valuable, for it is easy to confuse clinically Grade I or even Grade III lesions with a pure atrial septal defect.

Recent Reports and their Bearing on Clinical Diagnosis

Advances in cardiac surgery have made it plain that some atrial septal defects are more difficult to repair than others. In particular, endocardial cushion defects have proved both difficult and dangerous (Bailey *et al.*, 1954), though recent reports from the Mayo Clinic are encouraging (Kirklin *et al.*, 1955; Cooley and Kirklin, 1956). Hence the clinical recognition of these anomalies has taken on a new importance. Watkins and Gross report their experiences of the surgical repair of 43 cases of atrial septal defect, 4 of which proved to be endocardial cushion defects of either Grade I (e.g. their Fig. 3) or Grade II (e.g. their Fig. 2), all four with deformity of both mitral and tricuspid valves. Surgical closure of the ostium primum was achieved in some of these, only to be followed promptly by cardiac failure and death: they question the wisdom of closing an ostium primum that has been acting as an escape route for blood regurgitating through an incompetent mitral valve. Furthermore, dissection revealed that the bundle of His ran across the inferior margin of the defect, and was thus exposed to damage by surgical closure. Three speakers in the discussion following this paper said that surgical closure in Grade I defects not infrequently proved fatal, the third specifying complete heart block as a dangerous complication (Bailey, 1955; Lam, 1955; Lewis, 1955).

With regard to the clinical differentiation from pure atrial septal defects, Watkins and Gross think that an endocardial cushion defect may be suspected in a patient who presents with a thrill over the lower sternum and a harsh systolic murmur along either sternal border, but can be diagnosed with certainty only by digital exploration of the atrium. Blount *et al.* (1956) describe five patients with an ostium primum defect, in whom the diagnosis was confirmed at necropsy in 3 and at operation in 2, and discuss the diagnosis. One (Case 3) was unusual in that the A-V valves were normal and the heart was not specially large, but the other four evidently had Grade I or Grade II endocardial cushion defects. This diagnosis should be suspected in a patient who seems to have a severe atrial septal defect with, in addition, signs suggesting mitral regurgitation. The A-V valve in each instance formed the floor of the defect, the mitral valve being abnormal in 4 of the 5, and, the tricuspid in 2: the former was thought to be incompetent in all 4, and in 2 this was confirmed at operation. There was no evidence that the ventricular septum was defective in any of the 5 cases.

Wakai *et al.* (1956) report catheter studies of six children aged 5 months to 6 years and five adults aged 21 to 28 years. The presence of an endocardial cushion defect was confirmed in all at operation or necropsy but, with two exceptions, the precise type of defect is not stated. Most of them had a large pulmonary blood flow due to left-to-right shunts occurring both at atrial and (to a lesser extent) at ventricular levels. Three points were found to be of value in differential diagnosis. First, in 6 of the 9 cases (when the tip of the catheter had been manipulated into the left ventricle) the shaft was seen to lie much lower in the cardiac silhouette before traversing the septum than with a pure atrial septal defect. (Clearly, however, if there were an ostium secundum defect *also*, the catheter might traverse the septum at a higher level.) Secondly, evidence of a left-to-right shunt at both atrial and ventricular levels was found, again in 6 of the 9 cases. Thirdly, they found no preferential shunting of the venous blood from the *right* lung.

In one cyanotic girl studied recently, the catheter passed equally easily into the left ventricle or through the right ventricle into the pulmonary trunk with very little withdrawal and with very little change in the position of its shaft: so we thought that there was a common atrio-ventricular canal. This may be another useful point.

Toscano-Barbosa *et al.* (1956) report on the electrocardiographic findings in 16 proven cases of endocardial cushion defect, but again the extent of the individual defects is not defined. They found a basic uniformity that was modified only in the presence of pulmonary hypertension or of gross left ventricular hypertrophy due to mitral insufficiency; this may be of value in distinguishing this group from pure atrial septal defect.

Summary

The group of cardiac malformations that have in common defective development of the dorsal and ventral atrio-ventricular (A-V) endocardial cushions may usefully be called endocardial cushion defects. They can be divided into three grades: Grade III (persistent common A-V canal), Grade II (intermediate forms), and Grade I (persistent ostium primum). Two illustrative cases are described —a girl of 14 with a Grade III defect and other anomalies, and a woman of 38 with a Grade II defect, who died as a result of massive thrombosis within the pulmonary arterial tree.

The hæmodynamic disorder usually predominant in these patients is that due to the atrial septal defect. However, the picture may be complicated by any or all of the following: (1) incompetence of one or both A-V valves or of a common valve, (2) an additional left-to-right shunt at ventricular level, and (3) associated congenital cardiac anomalies (e.g. pulmonary stenosis). The recognition of incompetence of an A-V valve—usually the mitral—helps in differentiating between an endocardial cushion defect and a pure (and therefore—*ceteris paribus*—more easily operable) atrial septal defect. Cardiac catheterization and electrocardiography often help in making this distinction.

We think the possibility of a Grade III endocardial cushion defect should be considered more often in cyanotic patients whose diagnosis is uncertain.

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THE HÆMODYNAMICS OF MITRAL STENOSIS BEFORE AND AFTER COMMISSUROTOMY

BY

JANET DICKENS,* LUIZ VILLACA, ASHER WOLDOW, AND HARRY GOLDBERG

From the Brith Sholom Cardiopulmonary Laboratory, Department of Medicine, Hahnemann Medical College and Hospital, and The Bailey Thoracic Clinic, Philadelphia, Pennsylvania

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Clinical changes following mitral valvotomy are sometimes difficult to evaluate. The need for an objective method in assessing the effectiveness of surgery is apparent, and the value of combined heart catheterization in appraising the hæmodynamics of mitral stenosis has been reported (Goldberg *et al.*, 1955, 1956). A total of 58 patients have been studied by this procedure, 16 of them after as well as before mitral valvotomy. The importance of the combined technique can be readily appreciated, particularly in assessing the changes of pressure gradient and flow across the involved valve. Comparison of the data with those previously obtained by right heart catheterization alone has yielded significant differences and provides additional support for the continued use of this new technique.

Material and Methods

Sixteen patients, thirteen women and three men, were studied before and after mitral valvotomy. The diagnosis of pure mitral stenosis was confirmed by surgery in all patients. Mitral insufficiency was not produced in any case. Cardiac catheterization was repeated from twelve days to four months after operation.

Combined heart catheterization was performed in the post-absorptive state with premedication consisting of seconal 120 mg. and demerol 50 mg. Right heart catheterization was done in the usual manner except that the patient was placed in the prone position. After the pulmonary venous capillary pressure was recorded, the catheter was positioned in the right or left pulmonary artery close to the hilus. A Cournand needle then was placed in the brachial artery. Left heart catheterization was performed by the Fisher modification (Kent *et al.*, 1955) of the method originally described by Biörk (1953). Our experiences in 450 cases of left heart catheterization are described elsewhere (Bougas *et al.*, 1956; Musser *et al.*, 1956). With the aid of fluoroscopy, a 6-inch, 18-gauge, thin-walled needle (Becton and Dickinson) was introduced into the left atrium via the eighth or ninth intercostal space 4 cm. from the midline. A polyethylene or nylon catheter was inserted through the needle. Continuous monitoring of the pressure was done on an oscilloscope or poly-oscillograph (Sanborn) as the catheter was advanced into the left ventricle. All manœuvring then was halted until the control cardiac rate, rhythm, and blood pressure were re-established. At this time, expired air was collected in a Tissot spirometer during a 3-min. period, at the middle of which samples were withdrawn from the pulmonary and brachial arteries simultaneously. Pressures were immediately recorded as the catheter was withdrawn from the left ventricle to the left atrium to determine the ventricular filling pressure gradient. In five patients with atrial fibrillation, a second needle was inserted into the left atrium and simultaneous recordings were made from the left ventricle and left atrium during estimation of the cardiac output.

The cardiac output was calculated by the direct Fick method. Blood oxygen was determined according to the method of Van Slyke and Neill (1924). Respiratory analysis was done on the Pauling oxygen analyser. Pressures were measured by electromanometers and recorded on a poly-oscillograph (Sanborn). The zero

* Samuel Kardon Fellow in Cardiovascular Physiology; work done partly during tenure of National Heart Institute Fellowship.

level was taken as 5 cm. below the angle of Louis. Pressure gradients were measured by planimetric integration. The mitral valve area and pulmonary vascular resistance were calculated by a modification of the formulæ of Gorlin and Gorlin (1951), and right ventricular work was calculated as originally described (Gorlin, 1951).

$$\text{Mitral valve area, M.V.A. (cm.}^2\text{)} = \frac{\text{M.V.F.}}{31\sqrt{\text{V.F.G.}}}$$

where M.V.F. (ml./V.F.P. sec.) = C.O. (ml./min.)/V.F.P. × H.R.

and V.F.G. (mm. Hg) = $L.A._{v.f.p.} - L.V._{v.f.p.}$

Pulmonary Vascular Resistance, P.V.R. (dynes sec. cm.$^{-5}$) = $(P.A._m - L.A._m) \times 1332/C.O.$ (ml./sec.)

Abbreviations:

M.V.A. (cm.^{2})	= Mitral valve area
M.V.F. (ml./V.F.P. sec.)	= Mitral valve flow
V.F.G. (mm. Hg)	= Ventricular filling pressure gradient
V.F.P. (sec./beat)	= Ventricular filling period
H.R. (beats/min.)	= Heart rate
$L.A._{v.f.p.}$ (mm. Hg)	= Mean left atrial pressure during ventricular filling period
$L.V._{v.f.p.}$ (mm. Hg)	= Mean left ventricular pressure during ventricular filling period
C.O. (ml./min.)	= Cardiac output
P.V.R. (dynes sec. cm.$^{-5}$)	= Pulmonary vascular resistance
$P.A._m$ (mm. Hg)	= Mean pulmonary artery pressure
$L.A._m$ (mm. Hg)	= Mean left atrial pressure.

Results

Before Operation. Mitral valve flow was generally low, ranging from 59 to 190 ml./V.F.P. sec. (Table I). The flow was considered below normal (Goldberg *et al.*, 1956) (150 ml./V.F.P. sec.) in ten of the thirteen patients in whom it could be calculated before operation. It was less than 100 ml./V.F.P. sec. in four patients. The ventricular filling pressure gradient (V.F.G.) which was constantly observed, ranged from 5 to 26 mm. Hg. The mitral valve area was reduced in all patients, ranging from 0·5 to 1·3 cm.^{2}

The mean left atrial pressures were raised, ranging from 10 to 30 mm. In eight patients the left atrial pressure was greater than 20 mm. Hg. The pulmonary capillary pressures were above the upper limits of normal (12 mm. Hg) in eleven of the fifteen patients in whom this value was obtained, ranging between 10 and 32 mm. There was generally good agreement between the left atrial and capillary pressure tracings in both contour and magnitude. The end-diastolic pressure in the left ventricle was within normal limits (less than 10 mm. Hg) in all but one case, in which it was 12 mm. Hg.

The cardiac index was generally low, averaging 2·1 l./min./M^{2}BS (range: 1·4 to 4·5 l./min./M^{2}BS). In the patients in whom this value was reduced, the arteriovenous oxygen difference was increased.

The mean pulmonary artery pressure was raised in all but three patients: the rise was mild (20–25 mm. Hg) in two, moderate (26–39 mm. Hg) in five, and severe (greater than 40 mm. Hg) in six patients. The effective work of the right ventricle was increased in seven (greater than 1·0 kgM/min.) and within normal limits in six patients.

After Operation. (1) *Results Based on Response of Pressure Gradient and Mitral Valve Flow.* (*a*) Nine patients showed a significant fall in pressure gradient accompanied by a significant increase in flow, indicating improvement following surgery (Cases 1–9) (Table I) (Fig. 1). The mitral valve area increased in every case, ranging from 0·5 to 1·2 cm.^{2} before and from 1·8 to 4·3 cm.^{2} after operation. The mitral valve flow ranged from 59 to 150 ml./V.F.P. sec. before and from 155 to 304 ml./V.F.P. sec. after operation, increasing significantly in all patients.

The ventricular filling pressure gradient ranged from 11 to 26 mm. Hg before and from 3 to 13 mm. after operation. In eight patients in this group in whom the left atrial pressure fell significantly, the left ventricular end-diastolic pressure fell in three, remained unchanged in one, and rose

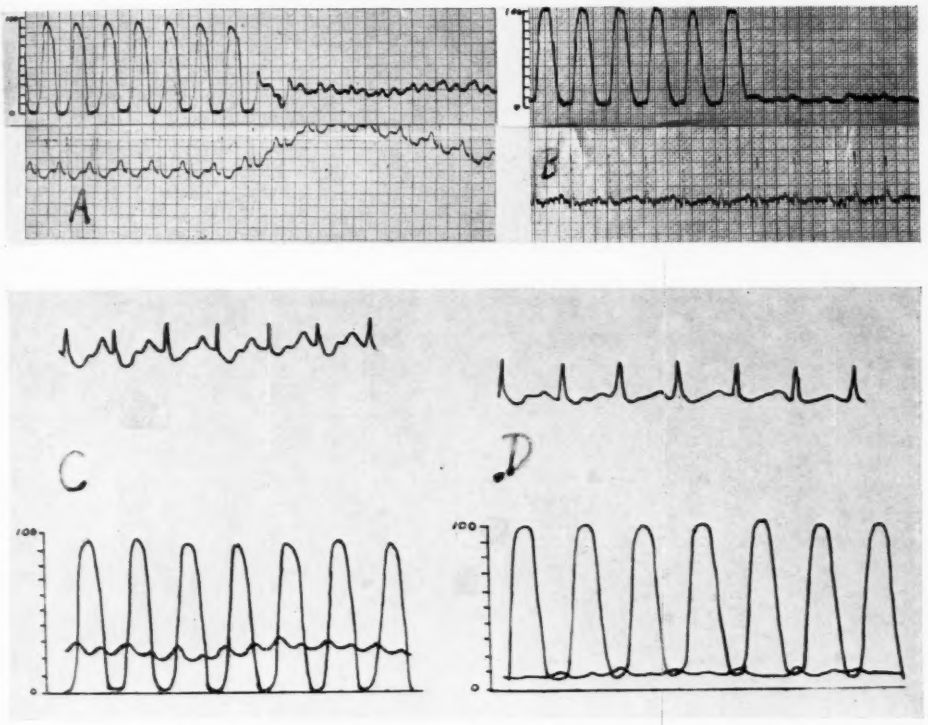

FIG. 1.—Case 8. *Above.* Continuous pressures recorded from the left ventricle to the left atrium (above), and electrocardiogram (below). (A) Before and (B) after mitral valvotomy. Note lower left atrial pressure. *Below.* Left atrial and left ventricular pressure tracings redrawn and superimposed, showing ventricular-filling pressure gradient. (C) Before and (D) after mitral valvotomy. Note decrease in pressure gradient. M.V.A. increased from 0·08 to 3·6 cm^2.

slightly (2–5 mm. Hg) in four. In one patient in whom the left atrial pressure was unchanged and remained within normal limits, the left ventricular end-diastolic pressure was increased from 0 to 9 mm. Hg.

Eight patients of this group had normal sinus rhythm. Before operation, the predominant wave in the left atrial tracing was the *a* wave in six patients and ranged from 21 to 48 mm. in height. The *a* and *v* waves were of equal prominence in the other two patients. After operation, the *a* waves decreased in all, ranging from 10 to 22 mm. in height. The *a* and *v* waves were of approximately equal magnitude in five cases while, in the remaining three, the *a* wave was still predominant.

In the eight patients with normal sinus rhythm, the ventricular filling period per beat ranged from 0·24 to 0·38 sec., averaging 0·30 sec. before, and from 0·16 to 0·27 sec., averaging 0·21 sec. after operation. The filling period decreased in six patients, in whom the cardiac rate at the time of the post-operative study was unchanged in three, increased in two, and decreased in one. The filling period was unchanged in the remaining two patients.

The cardiac index was below normal in all but one of the patients in this group, rising after operation in eight and to within normal limits in seven of them. In one, there was no change. The arteriovenous oxygen difference decreased after operation by at least 1 vol. per 100 ml. in all but two patients, in one of which the cardiac index had increased only slightly.

The mean pulmonary artery pressure varied considerably before operation and fell significantly

TABLE I

PHYSIOLOGIC DATA BEFORE AND AFTER MITRAL VALVOTOMY

Case No.		Oxygen consumption (ml./min.)	Arterio-venous oxygen difference (vol. %)	Cardiac output (l./min.)	Cardiac index (l./min./M²BS)	Heart rate (beats/min.)	Pulmonary circulation						Systemic circulation						
							Pressures (mm. Hg)				Pulmonary vascular resistance (dynes sec. cm.⁻⁵)	Right ventricular work (kgM/min.)	Pressures (mm. Hg)			Left ventricular filling period (sec./beat)	Left ventricular filling* pressure gradient (mm. Hg)	Mitral valve flow ml./V.F.P. sec.)	Mitral valve area (cm.²)
							Right atrium (mean)	Right ventricle S/D	Pulmonary artery S/D (mean)	Pulmonary capillary (mean)			Left atrium (mean)	Left ventricle S/D	Brachial artery S/D (mean)				
1	Before	205	4·6	4·4	2·5	108	0	20/0	23/12 (18)	12	127	0·65	11	92/0	116/76 (80)	0·28	15	145	1·2
	After	217	3·4	6·4	3·8	108	—	—	20/8 (11)	10	13	0·60	10	94/9	105/52 (80)	0·20	5	296	4·3
2	Before	148	4·7	3·1	1·9	110	0	32/0	27/13 (19)	15	155	0·53	13	96/0	110/70 (90)	0·24	12	117	1·1
	After	166	3·7	4·5	2·9	98	2	30/2	30/8 (18)	7	213	0·75	6	98/4	116/58 (72)	0·27	4	171	2·9
3	Before	124	4·1	3·0	2·1	100†	0	35/0	37/11 (29)	16	186	0·88	22	98/10	110/60 (80)	0·27	11	110	1·0
	After	169	3·3	5·1	3·7	100†	5	28/10	30/9 (19)	8	158	1·01	9	108/7	133/77 (114)	0·27	3	188	3·8
4	Before	164	4·6	3·6	2·3	123	10	—	45/28 (35)	28	200	1·15	26	94/5	114/60 (70)	0·24	19	122	0·9
	After	164	3·3	5·0	3·2	127	—	—	30/15 (20)	13	160	0·92	10	108/5	110/80 (90)	0·17	6	234	3·2
5	Before	156	5·3	2·6	1·7	80	—	—	50/20 (30)	19	368	0·73	18	94/4	106/68 (80)	0·38	12	87	0·8
	After	172	5·0	3·4	2·3	110	0	44/2	46/23 (30)	10	425	1·00	12	100/6	120/64 (84)	0·20	5	155	2·3
6	Before	187	4·5	4·2	2·8	108	6	70/6	70/43 (58)	30	533	2·35	30	96/10	104/63 (80)	0·37	26	106	0·7
	After	205	3·2	6·4	4·1	130	7	23/7	35/21 (28)	—	188	1·65	13	100/1	114/78 (86)	0·16	13	304	2·8
7	Before	144	6·9	2·1	1·4	100	—	100/10	100/48 (60)	27	1181	1·21	29	90/8	112/74 (80)	0·36	15	59	0·5
	After	166	4·1	4·0	2·7	99	4	67/6	70/28 (50)	15	740	1·94	13	104/10	128/74 (90)	0·24	9	168	1·8
8	Before	232	6·0	3·9	2·3	114	5	53/5	50/35 (40)	22	308	1·32	25	96/0	130/70 (100)	0·26	20	125	0·8
	After	170	4·5	3·8	2·3	100	0	20/0	18/5 (10)	3	42	0·33	8	103/5	—	0·17	4	226	3·6
9	Before	198	6·7	3·0	2·0	95†	7	70/5	78/32 (49)	26	560	1·40	28	104/10	129/83 (104)	0·21	16	150	1·2
	After	215	4·5	4·8	3·0	106†	5	45/0	52/22 (38)	—	400	1·60	14	148/3	150/80 (108)	0·20	8	226	2·7

9	Before	198	6·7	3·0	2·0	95†	7	70/5	78/32 (49)	26	560	1·40	28	104/10	129/83 (104)	0·21	16	150	1·2
	After	215	4·5	4·8	3·0	106†	5	45/0	52/22 (38)	—	400	1·60	14	148/3	150/80 (108)	0·20	8	226	2·7
10	Before	135	5·2	2·6	1·7	94	0	28/0	35/15 (20)	10	305	0·49	10	90/5	120/70 (80)	0·32	6	88	1·2
	After	221	2·9	7·6	4·9	105	6	42/5	48/26 (35)	16	168	2·46	19	100/10	126/62 (82)	0·26	7	282	3·5
11	Before	182	6·8	2·7	1·5	105†	6	28/7	26/18 (19)	16	237	0·41	11	105/6	120/70 (80)	0·28	6	95	1·3
	After	171	6·1	2·8	1·7	117†	5	30/4	30/12 (22)	8	286	0·54	12	110/10	138/68 (88)	0·18	5	136	1·9
12	Before	132	8·3	—	—	60†	5	42/4	42/20 (26)	12	—	—	10	89/3	95/70 (84)	0·43	7	—	—
	After	176	8·7	2·0	1·2	100†	10	65/10	60/40 (42)	21	1000	0·73	17	94/8	115/68 (80)	0·35	8	57	0·7
13	Before	178	7·7	2·3	1·4	132†	12	82/11	99/27 (60)	—	1145	1·22	24	110/12	120/86 (96)	0·17	8	104	1·2
	After	170	6·0	2·8	1·8	126†	9	—	40/18 (35)	22	570	0·91	15	93/4	125/80 (80)	0·20	5	111	1·5
14	Before	218	—	—	—	124	4	38/7	38/20 (28)	14	—	—	18	112/9	136/78 (94)	0·24	12	—	—
	After	216	3·9	5·6	3·3	108	7	32/11	30/10 (20)	10	14	0·95	19	116/17	140/80 (98)	0·24	4	217	3·5
15	Before	189	3·0	6·3	4·5	118	4	62/8	60/30 (41)	32	203	2·65	25	115/4	118/62 (75)	0·29	24	190	1·3
	After	172	4·4	3·7	2·6	112	—	50/10	40/25 (31)	—	125	1·16	15	100/12	120/64 (74)	0·32	5	103	1·5
16	Before	145	—	—	—	123†	4	30/2	32/15 (22)	10	—	—	10	88/4	110/70 (82)	0·27	5	—	—
	After	167	5·2	3·2	2·0	90†	2	22/2	24/8 (14)	4	253	0·40	4	88/1	102/60 (68)	0·32	3	112	2·0

* Measured by planimetric integration.
† Atrial fibrillation present.

in four, moderately in one, and slightly in one. It remained essentially unchanged in three. Although the pulmonary vascular resistance fell significantly in four patients, it remained above normal in two of these. In one patient with a raised resistance before operation, there was no significant change. In those in whom the resistance was within normal limits before operation, it remained so afterwards.

In five patients, the right ventricular work was above 1·0 kgM/min. before operation: in three it fell significantly, in two to within normal limits. After operation it was greater than 1·0 kgM/min. in three patients; the mitral valve flow in these three had increased considerably following surgery, contributing in part to the increased work of the right ventricle.

(*b*) Two patients showed an increase in mitral valve flow with little change in pressure gradient. Possibly Case 10 improved since there was a large increase in the mitral valve flow with no increase in pressure gradient. The increase in cardiac output was accompanied by a fall in arteriovenous oxygen difference. The large increase in flow was probably responsible for the rise in the left ventricular end-diastolic pressure, left atrial, and pulmonary artery pressures, and right ventricular work. The data on Case 11 probably reflect little improvement physiologically at this time: there was no change in pressure gradient and only a moderate increase in mitral valve flow with consequent little change in mitral valve area; the arteriovenous oxygen difference was unchanged as were the left atrial and pulmonary artery pressures.

(*c*) Case 13 showed little change in mitral valve flow, pressure gradient, and mitral valve area. Right heart catheterization data in this patient did not reflect the poor response, and the mechanism of the fall in pulmonary artery pressure in this case is not clear.

(*d*) Three patients must be considered individually since their pre-operative data were not complete. In Case 14 the mitral valve flow and area after operation were well within normal limits, while the filling pressure gradient, obtained before and after operation, fell significantly, and the mean pulmonary artery pressure decreased slightly. The data, although incomplete, suggest improvement following surgery.

The data obtained in Case 12 indicate a poor result. The pressure gradient was unchanged after operation. The mitral valve flow was much reduced from the normal value while the arteriovenous oxygen difference was higher; and the mean left atrial and pulmonary artery pressures rose. The response of Case 16 is difficult to evaluate without a knowledge of the mitral valve flow before operation. The calculated mitral valve area appeared adequate although after operation the mitral valve flow was low and the pressure gradient changed little: the mean pulmonary artery and left atrial pressures fell.

(*e*) In Case 15 both mitral valve flow and ventricular filling pressure gradient decreased significantly. The slight change in area precludes the assumption of improvement in this patient, but the mean left atrial and pulmonary artery pressures fell as well as the pulmonary vascular resistance and right ventricular work.

(2) *Results Based on Pulmonary Artery Response Following Surgery.* (*a*) Six of the sixteen patients showed a significant fall in the mean pulmonary artery pressure after operation. Before, the mean pulmonary artery pressure was raised moderately in one (35 mm. Hg), and greatly in five (40–60 mm. Hg). Of these six patients, mitral valve area increased significantly in four. These four also showed an excellent response of pressure gradient and flow following surgery: the remaining two (Cases 13 and 15) showed only a slight increase in mitral valve area and equivocal results in terms of pressure gradient and flow. In Case 13 the significance of the fall in the pulmonary artery pressure was questionable in the presence of a decrease in flow after operation.

(*b*) One patient (Case 9) showed only a moderate fall in the pulmonary artery pressure with an excellent response of gradient and flow after operation. The mitral valve area increased significantly and the left atrial pressure fell.

(*c*) Three patients showed a slight fall in the pulmonary artery pressure after operation. Although there are too few patients in this group to compare the response of the pulmonary artery pressure with that of gradient and flow, one (Case 3) showed an excellent response of gradient

and flow with an increase in valve area. Similarly, in Case 14, there was a large fall in the gradient and a normal mitral valve flow after operation. A third (Case 16) in this group showed no change in pressure gradient and still had a low flow.

(*d*) Three patients had an increase in pulmonary artery pressure after operation. In one (Case 10), the mitral valve area was increased significantly: there was a significant increase in mitral valve flow with no change in the pressure gradient and the mean left atrial pressure also increased. The increase in pulmonary artery pressure probably reflects the increase in flow.

In a second (Case 11), the slight rise in the pulmonary artery pressure from a normal value was accompanied by a moderate increase in the mitral valve flow with little change in the pressure gradient. The mitral valve area, however, was not increased much and the left atrial pressure was unchanged. In the third (Case 12), the pressure gradient was unchanged, but the mitral valve flow obtained only after operation was very low, and the mitral valve area was considered inadequate.

(3) *Results Based on Data Before Operation.* Analysis of the data based on mitral valve area or pulmonary artery pressure revealed little correlation with the response after operation in mitral valve area, flow, and pressure gradient or pulmonary artery pressure. Of three patients with normal resting pulmonary artery pressures before, two (Cases 2 and 1) showed a significant response of pressure gradient and flow, and an increase in area. One (Case 11) showed a poor response of pressure gradient and mitral valve flow with a slight increase in mitral valve area. Similarly, of six patients with severe pulmonary hypertension, the response of pressure gradient, mitral valve flow and area was excellent in four and poor in one: the sixth (Case 15) could not be assessed because the fall in pulmonary artery pressure was accompanied by a fall in flow.

Discussion

Before the application of combined heart catheterization to the study of mitral valvular disease, the physiological evaluation of the results of surgery in mitral stenosis was based upon reflected changes in the pulmonary circuit (Ferrer *et al.*, 1955; Werkö *et al.*, 1953; Janton *et al.*, 1952). With the availability of direct pressure-flow measurements across the mitral valve, it was hoped that a more accurate assessment of the changes could be made, and a comparison of results based on these measurements with those previously derived from observed changes in the pulmonary circulation could be made.

The present study indicates that an accurate appraisal of the changes in the functional orifice size following mitral valvotomy requires a knowledge of both pressure gradient and flow across the valve. Changes in pressure gradient alone at the time of surgery as advocated by some workers (Moscovitz *et al.*, 1955) are considered inadequate. From the data obtained, it can be seen that different interpretations become necessary when flow is known in patients with similar changes in pressure gradient. For example, a fall in pressure gradient signifying functional improvement can be appreciated in Case 1 who showed a large increase in flow as well. A fall in pressure gradient alone is misleading in Case 15 who had a decrease in mitral valve flow and little change in functional orifice size.

A comparison of Cases 10 and 13 shows that failure of the ventricular filling gradient to change following surgery does not always signify that the functional orifice was unchanged. Although Case 13 showed little change in gradient or flow and thus no change in valve area, Case 10 showed an increase in flow and area despite the small change in gradient.

In general, an unequivocally good response is indicated by a significant increase in flow accompanied by a significant fall in the pressure gradient. In such patients the functional valve area is always increased and generally the pressure in the left atrium is reduced. An increase in flow with no appreciable change in the pressure gradient may reflect functional improvement: evaluation of the surgical results is, however, difficult in such cases.

Patients who show little or no change in flow, gradient, and area represent a poor surgical result with little relief in the obstruction. One (Case 13) of the sixteen patients was classified this way. At surgery, the mitral orifice, finger-tip in size, was reported as increased to admit two fingers. A

second (Case 12) showed no change in gradient: the flow was not obtained before operation and was low afterwards; the mitral valve area was still considered inadequate; and the valve was finger-tip size before and a loose-finger size afterwards.

When a decrease in mitral valve flow occurs after operation, the results of surgery again are difficult to assess. Fall in flow may be due to a difference in the basal state of the patient, cardiac failure, production of mitral regurgitation, or inadequate relief of the obstruction.

The height of the pulmonary artery pressure and in particular the presence of pulmonary hypertension has been used as a measure of the severity of the disease, and a major indication for surgery (Baronofsky, 1953; Werkö *et al.*, 1953; Ferrer *et al.*, 1955). The present study discloses, however, that widely varying degrees of pulmonary artery pressure may be found with the same valve area or level of pressure gradient. When the degree of mitral obstruction and the pulmonary vascular resistance are constant, the pulmonary artery pressure varies with flow (Goldberg *et al.*, 1955). On the other hand, when the flow and mitral obstruction are constant, the level of pulmonary artery pressure varies with the degree of pulmonary vascular resistance. In the present group of patients, significant mitral obstruction was accompanied by normal, as well as severely raised pulmonary artery pressures. Although Case 1, one of the three patients with normal pressures in the pulmonary circuit, had minimal symptoms, Cases 2 and 11 complained of dyspnœa and fatigue and required digitalis therapy. Case 2 gave a history of transient atrial fibrillation and acute pulmonary œdema during pregnancy and Case 11 had a history of palpitation and congestive heart failure. The presence of pulmonary hypertension may not be the sole determining factor of the severity of disease or of the need for surgery in some cases when direct measurements of gradient and flow across the valve are known.

Evaluation of the changes in the pulmonary artery pressure following valvotomy, again necessitates the measurement of flow as well as pressure gradient. For example, Case 5, who had

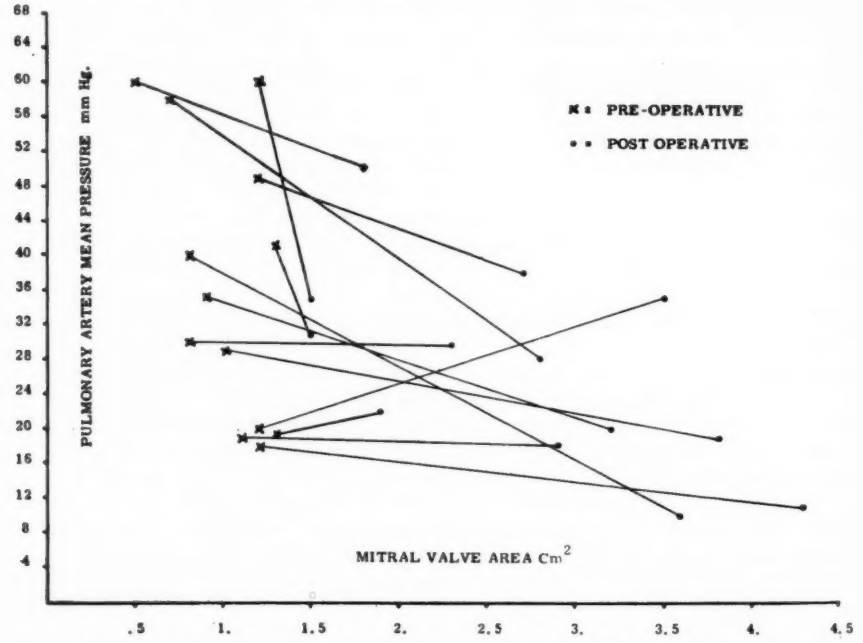

FIG. 2.—Relationship between the pulmonary artery pressure and mitral valve area before and after mitral valvotomy.

no change in the pulmonary artery pressure, showed an increase in mitral valve flow accompanied by a significant fall in ventricular filling pressure gradient and was considered to demonstrate physiological improvement following surgery that was not reflected by the pulmonary circulation. The frequently reported patient, who shows subjective and clinical improvement with little or no change in the data obtained by right heart catheterization, namely, the pulmonary artery pressure, may have to be re-investigated with this in mind.

A fall in the pulmonary artery pressure, considered alone, may be misleading also. This result in Case 15 may be explained entirely by the fall in flow, the mitral valve area increasing only slightly, and pulmonary resistance remaining normal. In other patients, the decrease in pulmonary artery pressure is not proportional to the degree of improvement as judged by changes in the pressure gradient and mitral valve flow.

In general, it may be seen that the pulmonary circuit does not always reflect the changes in the dynamics at the mitral valve. Although in many cases, relief of obstruction at the mitral valve is accompanied by a fall in the pulmonary artery pressure, the latter may change little following an adequate mitral valvotomy (Fig. 2). The persistence of pulmonary hypertension may be attributed to (1) increased pulmonary vascular resistance due to vascular changes and (2) an increase in flow relative to a restricted capacity of the pulmonary bed. On the other hand, a fall in pulmonary artery pressure may be explained entirely by a decrease in flow when the degree of mitral obstruction is affected little by surgery.

The pressure in the left atrium is a function of the degree of mitral obstruction and the magnitude of mitral valve flow. Although the elasticity factors of the atrium are of great importance in the presence of mitral obstruction, an adequate increase in the valve area is accompanied by a fall in the atrial pressure in most patients (Fig. 3), even in the presence of large increases in flow. Changes

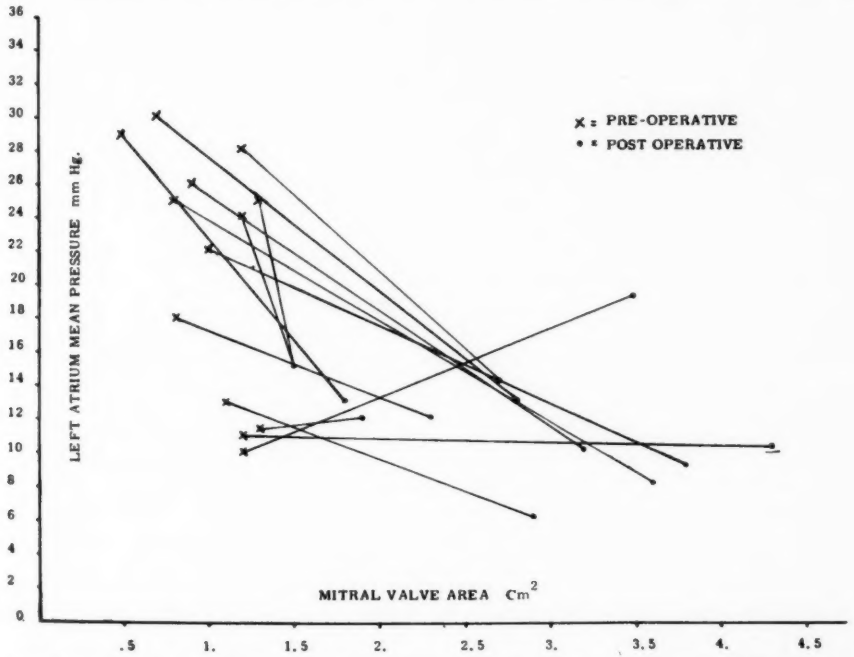

FIG. 3.—Relationship between the left atrial pressure and mitral valve area before and after mitral valvotomy.

in the left atrial pressure more closely parallel improvement following mitral valvotomy than do changes in the pulmonary artery pressure (Fig. 2 and 3).

Although a fall in left atrial pressure accompanying a fall in the ventricular pressure gradient is the usual response following relief of obstruction, a rise of the diastolic pressure in the left ventricle, as a result of better filling after operation, may account for a fall in gradient, e.g. Cases 1 and 14, in which the left atrial pressure remains unchanged. In these patients the changes in the left atrial pressure cannot be employed as a measure of improvement. Changes in left atrial pressure tracings in patients following surgery are of some interest. As one would expect, the *a* waves were much smaller in height in those patients who were classified as improved. The *v* wave becomes more prominent following surgery, suggesting relief of obstruction with rapid filling of the left ventricle. The pulmonary venous capillary pressure paralleled the changes in the left atrial pressures.

As previously established, the left ventricular filling period in mitral stenosis frequently includes a portion of the isometric contraction and relaxation phases of the cardiac cycle, and thus exceeds the limits of diastole (Moscovitz *et al.*, 1955). The changes in the ventricular filling period following mitral valvotomy are of interest. In patients with similar heart rates before and after surgery, a decrease in the ventricular filling period accompanied by a large increase in mitral valve flow is suggestive of relief of the obstruction. These patients had an excellent response to surgery based on the previously discussed criteria.

Since a decrease in the ventricular filling period accompanied by an increase in heart rate may be expected normally, such a change is difficult to assess. However, in patients with significant mitral valve obstruction, such a response would be accompanied probably by a fall in the mitral valve flow and/or a rise in ventricular filling pressure gradient and left atrial pressure. The decrease in the filling period in patients in whom there occurred both an increase in the mitral valve flow and a fall in the pressure gradient after operation would therefore seem to be significant despite an increased heart rate.

A decrease in heart rate results in a lengthening of the ventricular filling period. When the ventricular filling period was unchanged or decreased in the presence of a slower heart rate, and the response to surgery was otherwise considered good, this result would suggest that the filling period at a faster heart rate before operation was abnormally prolonged.

The changes in mitral valve area following surgery showed a good correlation with other findings in most instances. When the area was significantly increased, the mitral valve flow was always much increased and the left atrial pressure generally decreased. The pulmonary artery pressure generally fell or remained normal, but did not reflect the significant increase in area in all cases. In those patients with only slight increase in area, there were variable responses of mitral valve flow and left atrial and pulmonary artery pressures.

Mitral valve area in this group of patients was calculated both by the original Gorlin and the modified formulæ described above. A comparison of these areas shown in Table II reveals a number of discrepancies. Analysis of the values used in both formulæ reveals differences in both the ventricular filling period and, hence, mitral valve flow, and in the left atrial-left ventricular filling pressure gradient. The flows and areas are smaller as calculated by the original formula. The above discrepancies appear to be more striking after operation.

The "diastolic" filling period is consistently longer when obtained from the brachial artery pressure than directly from the left atrial and left ventricular pressure tracings. With the raised left atrial pressure before operation, this difference is frequently not striking and, hence, the mitral valve flows and areas do not differ significantly when calculated by either method. After operation, however, with the decrease in the left atrial pressure, the difference in the ventricular filling periods may be appreciable. In Cases 1 and 3 the ventricular filling periods obtained from the brachial artery tracings actually increase while they decrease when obtained directly from the left heart tracings. Hence, in these cases the discrepancy in mitral valve flows and areas may be considerable.

Frequently, the pressure gradient as calculated by the original Gorlin formula is larger than that measured directly from the pressure tracings. However, this is not too serious a difference

TABLE II

MITRAL VALVE AREA BEFORE AND AFTER MITRAL VALVOTOMY

Patient		Modified formula	Original formula	Surgeon's estimate*	Patient		Modified formula	Original formula	Surgeon's estimate*
1	Before	1·2	1·4	Tight f	9	Before	1·2	0·5	Less than f tip
	After	4·3	2·1	2 f		After	2·9	—	1¾ f
2	Before	1·1	1·5	f tip	10	Before	1·2	1·0	f tip
	After	2·9	2·9	1¾ f		After	3·5	2·1	1¾ f
3	Before	1·0	0·8	f tip	11	Before	1·3	0·5	Less than f tip
	After	3·8	2·4	2 f		After	1·9	1·0	2 f
4	Before	0·9	0·6	f tip	12	Before	—	—	f tip
	After	3·2	1·7	2 f		After	0·7	0·4	1 loose f
5	Before	0·8	0·6	Tight f tip	13	Before	1·2	—	f tip
	After	2·3	1·3	1¾ f		After	1·5	0·3	1¾ f
6	Before	0·7	0·7	Tight f tip	14	Before	—	—	f tip
	After	2·8	—	1½ f		After	3·5	2·3	1¾ f
7	Before	0·4	0·3	Less than f tip	15	Before	1·3	1·2	Tight f
	After	1·8	1·1	1½–1¾ f		After	1·5	—	1½ f
8	Before	0·8	—	f tip	16	Before	—	—	f tip
	After	3·6	†	1¾ f		After	2·0	†	2 f

* Surgeon's estimate—Dr. C. P. Bailey, in fingers (f).
† Pulmonary capillary pressure less than 5 mm. Hg.

since the square root of the gradient is employed in the calculations. Occasionally the pulmonary venous capillary pressure cannot be obtained due to technical difficulties, or may be less than 5 mm. Hg, as occasionally is observed following mitral valvotomy (Cases 8 and 16): the mitral valve areas cannot then be calculated by the Gorlin method.

A combination of the above factors in any individual case produces varying differences in the mitral valve area calculated by both methods, but in general those calculated by the Gorlin formula are smaller. This is of special interest in the evaluation of the surgical results since, in many cases, areas after operation calculated by the original formula may still appear inadequate and may actually suggest significant residual stenosis, but larger values are obtained in these patients when employing the direct left heart measurements.

This series is too small to predict the response to valvotomy from analysis of the physiological data before operation. Nevertheless, there was little difference in the hæmodynamic pattern before operation in those subjects exhibiting excellent, questionable, or poor responses. However, two patients who showed a poor response of gradient and flow afterwards had small flows and gradients before. It is of interest to note that the pulmonary artery pressure was much raised in one and within normal limits in the other. Valvular pathology and surgical technique undoubtedly play important roles in the final result.

The presence of myocardial insufficiency as the predominant abnormality is an important consideration in assessing the surgical results. However, in the absence of clinical failure, evaluation

of this factor is difficult, and even the presence of failure may be due to predominant mitral obstruction. The absence of pulmonary hypertension, as suggested by some workers (Ferrer *et al.*, 1955), does not exclude mitral obstruction as shown by combined heart catheterization, and normal pressure may exist in the presence of significant mitral stenosis. These patients may respond with an excellent surgical and physiological result, as shown by the above data.

From the present study, it can be seen that data obtained by right heart catheterization alone are frequently inadequate or even misleading in an individual case: estimation of the degree of stenosis cannot always be made on the basis of indirect measurements of the pulmonary circulation. The demonstration of a pressure gradient across the mitral valve establishes unquestionably the diagnosis of mitral stenosis. The simultaneous measurement of mitral valve flow and pressure gradient by combined heart catheterization not only permits estimation of the severity of the obstruction, but also allows for a more accurate estimation of the degree of improvement following mitral valvotomy.

Summary

Sixteen patients were studied before and after mitral valvotomy by combined heart catheterization. Measurement of the ventricular filling pressure gradient alone is inadequate in assessing the results of valvotomy since the changes in flow significantly influence the hæmodynamics, and may lead to erroneous interpretations.

The response is considered excellent when there is a significant increase in the mitral valve flow accompanied by a significant fall in the left ventricular filling pressure gradient. Those patients who show an increase in flow with little change in gradient need further evaluation. Those who are considered to have done poorly revealed little change in either.

The pulmonary artery pressure in general falls when there is a good response in pressure gradient and in mitral valve flow and area. However, the changes are not always parallel. The pulmonary artery pressure may change little in spite of a fall in pressure gradient and an increase in flow and functional valve area. Hence, in the individual patient, a knowledge of both flow and pressure gradient is essential in judging the significance of the changes in the pulmonary artery pressure.

The left atrial pressure generally falls with an adequate increase in mitral valve area. Areas calculated by the original Gorlin formula frequently indicate residual mitral stenosis after operation while the modified formula more adequately reflects the increase in functional orifice size.

Analysis of data before operation in this small series reveals little information as yet upon which to predict the result of the operation. A normal resting pulmonary artery pressure may be found in the presence of a significant degree of stenosis and a good surgical result may be obtained in these patients.

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SINO-AURICULAR BLOCK ASSOCIATED WITH INTRA-THORACIC NEW GROWTHS

BY

PAGET DAVIES

From King's College Hospital

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In 1930 Fishberg discussing the clinical syndromes arising from tumours of the heart observed that such tumours were usually asymptomatic: even when symptoms were present, diagnosis before necropsy was never definite. Seven years later eight examples of various cardiac arrhythmias associated with intrathoracic new growths were reported by Van Nieuwenhuizen and Kamerling (1937). Discussing cardiac arrhythmias due to bronchial carcinoma in 1944, Pearson found an incidence of arrhythmias of 10·6 per cent in his series of 66 patients. The diagnosis was proved by necropsy in 51 of these patients, and invasion of the atrium had occurred in each of the patients with an arrhythmia and in one other—an incidence of 12 per cent.

Most writers on the subject (Fishberg, 1930; Yater, 1931; Van Nieuwenhuizen and Kamerling, 1937; Scott and Garvin, 1942; Rusby and Thompson, 1943; Pearson, 1944; and Robertson and Russell, 1950) have stressed the importance of such arrhythmias chiefly as an occasional presenting symptom of a growth or as an indication of its spread to the heart and hence inoperability. In 1937, however, Van Nieuwenhuizen and Kamerling, having found in some of their patients evidence of sympathetic stimulation, suggested that a cardiac arrhythmia might result from irritation of the cardiac branches of the vagosympathetic nerves.

Two patients, each with sino-auricular block due to irritation of the vagus nerve by growth, are now described.

Case Records

Case 1. The patient, a man of 55 years, was first seen by his medical attendant complaining of hoarseness which persisted until his death a year later. Previously he had been a fit man apart from winter bronchitis.

During August, 1951, he developed nausea and flatulence and became afraid to eat. In the first week of January, 1952, he had a seizure while at work. Similar attacks occurred from then onwards—as many as twenty in a day. On admission to hospital in February, 1952, he was found to have lost two stones in weight. He had a hoarse voice from a complete abductor paralysis of the left vocal cord. The heart rate was 70 a minute and the rhythm regular. The rate increased on exercise to 90–100 a minute but was not slowed by carotid sinus pressure. The heart size, impulse, and sounds were normal. The blood pressure was 110/90 mm. Hg in each arm. Clinically the nervous, respiratory, and gastro-intestinal systems appeared to be normal.

His major seizures occurred at any time. The patient found that over-breathing precipitated the attacks which were preceded by nausea and retrosternal tightness and followed by loss of consciousness. In the attacks, the upper limbs showed clonic movements and consciousness was lost for two to three minutes during which there was occasional incontinence of urine. The heart first slowed and then stopped for about ten to twenty seconds before returning to normal rate and rhythm. During the attacks, auricular pulsations were never seen in the neck veins, nor were heart sounds to be heard. With the return of consciousness, the head and neck became flushed but otherwise no sequelæ were observed. Both memory and behaviour were unaffected.

Investigations. Fluoroscopy revealed a mass in the superior mediastinum which did not pulsate but which obstructed the œsophagus at the level of the carina. During one examination, the patient lost

consciousness and complete standstill and dilatation of the heart was observed for about ten seconds. Tomograms confirmed the presence of a mass extending from the hilum of the left lung in front of and above the aortic arch.

Electrocardiographic records during attacks showed initial slowing followed by complete standstill of the heart. Recovery was initiated by ventricular escape, followed by an auricular rhythm from an ectopic focus with inversion of the P wave. Restoration of the normal rate and rhythm occurred at varying times: in the record shown (Fig. 1) after a standstill of twenty-one seconds. Electrocardiograms between attacks were normal. An electroencephalogram during an attack was probably normal allowing for superimposed muscle waves. Both the Wasserman and Kahn reactions were negative. At bronchoscopy and œsophagoscopy, no abnormality was detected.

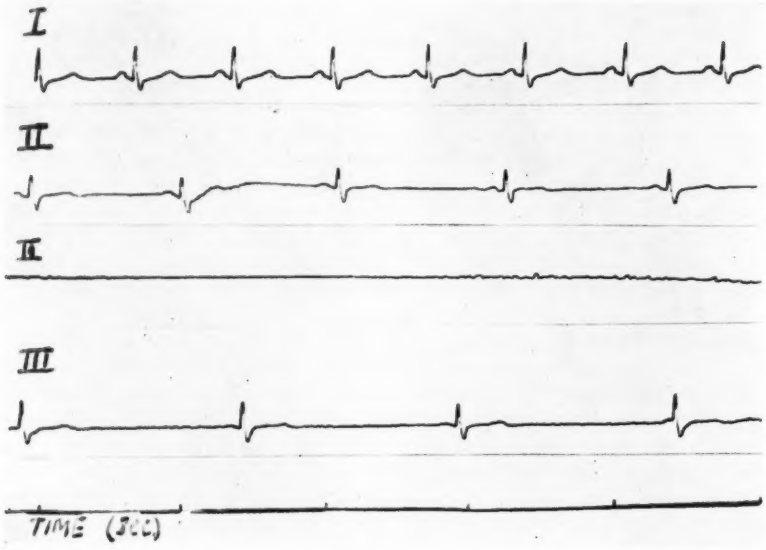

FIG. 1.—Case 1. Cardiogram taken during an attack, showing sino-auricular block. All records are lead II and not as marked.

Course. The syncopal attacks were seen on many occasions and always followed the same pattern. As the electrocardiographic findings pointed to sino-auricular block as the cause, he was given atropine 1/100 gr. sublingually four-hourly. The attacks rapidly diminished in number and ceased after eight days. Soon afterwards, however, two small subcutaneous nodules were noticed in the chest wall. These were excised and found to be metastatic deposits of an anaplastic carcinoma.

Two weeks later, the patient developed a cought with purulent sputum, fever, and a palpable pleural rub in the left axilla. Radiographs of the chest revealed extensive infiltration of both upper lobes. A few days later the seizures recurred, together with stridor, cyanosis of the head, and engorgement of the neck veins. Despite the use of atropine, he died in an attack on March 30, 1952.

Necropsy. There was a carcinoma of the right anterior basal bronchus. The hilar lymph nodes were enlarged, being replaced by growth, much of which was necrotic. The left vagus nerve entered these nodes, but its course and that of its recurrent branch could not be traced. The pericardium and heart together with its conducting system were intact and the brain was normal.

Histology. The tumour was an oat-celled bronchial carcinoma infiltrating the hilar lymph nodes and both upper lobes. Sections of the hilar mass showed several nerves surrounded by the growth and the left vagus nerve was seen to be infiltrated by carcinoma cells. Six centimetres above the site of the compression and invasion by the tumour, the left vagus nerve showed no evidence of Wallerian degeneration.

Case 2. This patient who attended King's College Hospital in 1921 had had radiotherapy for a lymphosarcoma affecting the cervical lymph nodes. He then developed seizures resembling Morgagni-Adams-Stokes' attacks. They occurred without warning and even during sleep. The patient would attempt to get out of bed and then would become still. In attacks, no pulse was felt and no heart sounds heard for about half a minute. Then movements of the upper limbs with stertorous breathing occurred. On recovery the patient appeared dazed but the pulse was slow and regular in rhythm. No evidence of heart block either clinically or electrocardiographically was found between seizures. An electrocardiogram was not obtained during a seizure. Tincture of belladonna diminished the frequency of the attacks but the patient eventually died during one three months later.

Necropsy. A mass of growth extended from the left jugular foramen to the apex of the lung. Into this mass, the left vagus nerve entered. On the right side of the neck, a further mass was present to which the right vagus nerve was adherent. The nerve, however, was not invaded. There was a left pleural effusion whilst the left lung contained an indefinite mass of growth. Both lower lobes showed bronchopneumonia. The pericardium, heart, aorta, and brain were normal.

Histology. Sections of the tumour were reported as showing a lymphosarcoma but unfortunately were not available for study.

Discussion

Intrathoracic new growths may cause cardiac arrhythmias in two ways—directly by invasion of the myocardium or the conducting tissue or both, and indirectly by affecting the vagosympathetic pathways to the heart. The former is much the commoner. Pearson (1948) in a review of malignant metastases in the myocardium, described 148 cases with bronchial carcinoma, 98 of which were proved by necropsy. Seven of these had been reported previously (Pearson, 1944). Invasion of the heart occurred in 17 (11·5%) and in approximately two-thirds of these an arrhythmia occurred. This was said to be due to invasion of one or both atria by growth. Reviewing 28 examples of cardiac arrhythmias associated with bronchial carcinoma of which 20 came to necropsy, Pearson (1950) found only four with an intact pericardium and heart, and three with only the pericardium affected. The growth had invaded one or both atria in all the others.

Although extensive infiltration of the mediastinum by growth is common, cardiac arrhythmias that can be attributed to an effect upon the vagus and sympathetic nerves are rare. Bruce Pearson (1945, 1950) reported a patient with bradycardia and attacks of cardiac asystole in which atropine had no effect. At necropsy, the vagi were enmeshed in mediastinal growth from a carcinoma of the bronchus. The obvious explanation is that the arrhythmia was due to vagal stimulation by growth but this is most unusual and in any case atropine did not control the arrhythmia.

Carcinoma of the bronchus, by virtue of its frequency and position, is the commonest intrathoracic tumour to cause cardiac arrhythmias. Other intrathoracic new growths are only occasionally responsible. Pearson (1944, 1948) mentioned one instance of mediastinal lymphosarcoma leading to auricular fibrillation while Van Nieuwenhuizen and Kamerling (1937) recorded another of cancer of the œsophagus with paroxysmal sinus tachycardia.

Of the cardiac arrhythmias described, auricular fibrillation is by far the commonest. Thus Van Nieuwenhuizen and Kamerling (1937) found in their patients that six had auricular fibrillation, one sinus tachycardia, and the other paroxysmal ventricular tachycardia. Three of these patients had evidence of sympathetic irritation in a dilated pupil on the same side as the tumour, and one also had exophthalmos. Pearson (1944) in his series reported four patients showing paroxysmal auricular fibrillation, one paroxysmal auricular fibrillation and flutter, one paroxysmal premature systoles, and one a persistent regular tachycardia.

Few examples have been reported of sino-auricular block in any of its forms (Cowan, 1939) and there is little doubt that they comprise the rarest types of arrhythmia due to growths in the thorax. A patient who had a variety of arrhythmias was reported by Mahaim and Gander (1947). Premature ventricular systoles and auriculo-ventricular nodal rhythm were recorded and in addition to these, the patient had seizures in which the heart stopped for five to ten seconds. These seizures

were controlled by belladonna. Later auricular flutter appeared and the seizures ceased. At necropsy, there was transpericardial spread of growth into the right atrium and destruction of the sino-auricular node but the auriculo-ventricular node and bundle were intact. The authors suggested that irritation by growth of the cardiac branches of the vagus nerve as they coursed over the surface of the heart was responsible for the attacks of cardiac asystole. Later destruction of these nerves by growth and spread to the right atrium was held responsible for the cessation of these attacks and the appearance of auricular flutter in which the ventricular rate was 140–150 a minute. Hence there was neither clinical nor pathological evidence of destruction of the A-V node and bundle. In 1945 Mahaim thought that stimulation of the vagus nerve by growth might well cause attacks of A-V nodal rhythm, but he could not find any recorded examples in which the sino-auricular node was intact, nor do such cases appear to have been recorded since then.

In both patients described in this paper, the left vagus nerve was enmeshed in growth and during the latter part of their illnesses, both patients suffered recurrent attacks of syncope due to sino-auricular block. In Case 1, the attacks were preceded by sinus bradycardia and recovery was initiated by ventricular escape. A similar march of events occurred in Case 2. In both patients, atropine prevented these attacks. It may thus be concluded that the attacks of sino-auricular block were due to vagal stimulation and that involvement of the left vagus nerve in the tumour mass was the determining cause. If this explanation in these cases is correct, then they are examples of a little recognized mechanism.

The evident rarity of sino-auricular block arising in such a way raises two further problems. One is the reason for this rarity in view of the frequency with which malignant tumours in the mediastinum encircle the nerve trunks. The other is to account for the intermittent nature of the attacks. Perhaps the former depends upon the early destruction of the functional activity of the nerve by growth and the latter upon an enhanced susceptibility to physiological fatigue. In any case, escape from vagus control will occur owing to a rise in venous pressure stimulating the cardio-accelerator mechanism (McDowall, 1926).

Summary

Two patients are described with recurrent syncope due to stimulation of the left vagus nerve by malignant tumours. Atropine prevented the attacks for a time but both patients eventually died in an attack.

Sino-auricular block is one of the rarest of the cardiac arrhythmias complicating intrathoracic tumours.

I wish to thank Dr. Clifford Hoyle and Dr. Terence East for permission to publish Cases 1 and 2 respectively and for their advice and criticism in the preparation of this paper.

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CASE REPORTS

CALCIFIED CARDIAC ANEURYSM

BY

W. J. HANBURY

From the Department of Pathology, St. Bartholomew's Hospital

An account of calcified cardiac aneurysms and a summary of previously reported cases has been given by Epstein (1953), who found only 37 instances of myocardial calcification reported during the present century, and in 26 of these the calcification occurred in a ventricular aneurysm. In 15 of the 26 cases a history of coronary thrombosis was obtained, the survival time after the acute attack ranging from five to eighteen years, while in the case presented by Epstein the patient was still living twenty years after the acute episode. It was also pointed out that the presence of calcification in cardiac aneurysms and infarcts was associated with relative longevity. Two further examples have been reported by Broustet *et al.* (1954) and by Aravanis and Luisada (1955).

The case now presented is remarkable in that the patient survived for 28 years after the original attack of cardiac infarction, and the degree of calcification found in the aneurysm and in the coronary arteries was very advanced. In view of this exceptionally long history, the apparent rarity of the condition, and the clearly defined pathological features, it was thought desirable to put on record a brief account of this patient.

Case History

The patient, a man, aged 80, and a member of the medical profession, had suffered from an attack of coronary thrombosis in 1927 at the age of 52 and had been treated by prolonged rest in bed. He had continued subsequently to have moderate breathlessness and angina of effort, and there was an exacerbation of these symptoms in 1940 when he was aged 65 but clinical examination at that time did not suggest a further infarct, while the electrocardiogram showed evidence of only an old defect. The angina of effort persisted, but no other serious episode occurred until 1955 when he had severe dyspnœa and blood-stained sputum together with acute retention of urine. He was admitted to a local hospital where, he was found to be cyanosed and gasping for breath, with a pulse rate of 120 a minute, a blood pressure of 115/60 mm. Hg, and a temperature of 99° F. There were clinical signs of cardiac enlargement with an apical systolic murmur, and coarse râles were heard all over the chest. The urinary retention, which was due to an enlarged prostate, was relieved by an in-dwelling catheter.

The patient was transferred to this hospital and was still cyanosed and breathless. Clinical examination revealed no enlargement of the heart, but there was a systolic murmur at the apex conducted to the axilla; there was pre-systolic gallop rhythm, the pulse was regular with a rate of 100 a minute, and the blood pressure was 130/90 mm. Hg. Crepitations and coarse râles were present all over the lungs, and slight œdema of the legs was noted. The blood urea was 76 mg. per 100 ml., the hæmoglobin 78 per cent (Haldane), and the white blood count 18,000 per cu. mm. with 94 per cent neutrophil polymorphs. Radiological examination of the chest was carried out in the ward, owing to the patient's poor condition, but was unsatisfactory as much of the heart shadow was obscured by the diaphragm, and only in retrospect was the outline of the cardiac aneurysm distinguished. The cardiogram showed sinus tachycardia, and an old apical myocardial infarct was indicated by loss of R in V5 with T inversion in V7. More recent posterior infarction was also indicated by pathological QS in III and Q in VF with S-T elevation.

The clinical diagnosis was congestive heart failure due to myocardial infarction. Rapid deterioration followed and death occurred ten days later.

Pathological Findings. The pericardium was normal except for firm fibrous adhesions over the cardiac apex. The heart weighed 520 g., and all the cavities were somewhat dilated and contained dark red

post-mortem blood clot. The valves and orifices were normal except for slight atheromatous thickening of the aortic valve. At the apex of the left ventricle the myocardium was reduced in thickness to 0·2 cm. over an area 4·5 cm. in diameter, with the formation of a slight, aneurysmal bulge. The wall of the aneurysm was hard and rigid due to extensive calcification (Fig. 1) and the sac was completely filled by adherent thrombus. There was also evidence of a more recent infarction of the left ventricle in a high posterior position, the myocardium being softened and discoloured over an ill-defined zone of approximately 2·5 cm. in diameter and covered internally by mural thrombus. The coronary arteries showed very advanced atheroma with extensive calcification (Fig. 1) and narrowing of their lumina, and the right coronary was occluded 10 cm. from its origin by a small red thrombus.

Histological examination shows the wall of the aneurysm (Fig. 2) to be composed of dense hyaline fibrous tissue, with areas of calcification and very few remaining muscle fibres. The adherent thrombus shows hyaline change in its deeper layers. The posterior left ventricular wall shows evidence of both old and recent infarction, with areas of fibrosis as well as hæmorrhagic zones where there are necrotic muscle fibres and infiltrations of inflammatory cells.

Apart from the heart, other changes found post mortem included œdema of the lower limbs, bilateral pulmonary congestion, œdema, and organizing pneumonia; a mild grade of chronic venous congestion of the liver; fairly severe generalized atherosclerosis; and senile enlargement of the prostate.

FIG. 1.—X-ray photograph of the heart at necropsy, showing calcification of the aneurysm and of the coronary arteries.

FIG. 2.—Photomicrograph of the wall of the aneurysm, showing fibrous tissue with calcium deposits and remnants of muscle fibres. The mural thrombus (stained darkly, above) and the pericardium with a coronary artery are also shown. Hæmatoxylin and eosin. ×15. The section was not decalcified.

Summary

A brief presentation has been made of a case of calcified left ventricular aneurysm in a man, aged 80, with an exceptionally long history dating from cardiac infarction occurring 28 years previously. A search for published records of similar cases showed that myocardial calcification, with or without aneurysm formation, is uncommon.

I am indebted to Dr. E. F. Scowen and Professor J. W. S. Blacklock for their help and advice, to Dr. R. S. Duff for the electrocardiographic report, to Dr. G. S. Sansom for the photomicrograph, and to Mr. J. W. Miller for histological sections.

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ABSENCE OF PULSE IN BOTH UPPER EXTREMITIES DUE TO AN AORTIC ARCH ANOMALY

A. C. AZEVEDO, R. ROUBACH, A. A. DE CARVALHO, A. NEY TOLEDO, AND W. ZANIOLO*

From the Hospital N.S. das Vitorias, Rio de Janeiro

The absence of pulses in both upper extremities, with normal or increased pressure in the lower ones, has been known as the so-called " pulseless disease " or Takayasu disease.

In the reported cases, the cause was an arteritis of the aortic arch and, although mentioned as a possibility, no case due to an aortic arch anomaly has been described.

In the case to be reported, the absence of pulses was due to a rather unusual anomaly of the aortic arch.

Case Report

A 30-year-old man was admitted to the hospital ward with a right-sided hemiplegia, already improving. He was leading a normal life, working as a radio-operator, until 11 days before admission, when he complained of dizziness and headache, and after a few days woke up in the morning unable to walk or talk. Since then, he had improved rapidly. He had been admitted to hospital, when 15 with a diagnosis of heart disease. We were unable to obtain any further data on this previous examination. His father and a brother died of " cerebral apoplexy".

He was well developed, but there was difficulty of movement and speech due to the right hemiparesis. There was an easily visible and palpable collateral circulation in the back, more marked in the right intercostal spaces. Pulses were unobtainable in both upper extremities, while easily and forcibly palpable in both carotid arteries and legs. Blood pressure could not be registered in either arm by the auscultatory method. An external recording of the pulses was made, showing a marked delay and " rounding " of the arm curves (Fig. 1). The intra-arterial pressure (Fig. 2) was recorded in both carotid arteries, both femoral arteries, and the left radial artery, and was high and of normal contour in the legs and in the neck, and greatly diminished in the arm, with an abnormally delayed anacrotic limb. During the puncturing of the radial artery the jet of blood was continuous and very weak.

The apex beat was strong and located at the fifth intercostal space, at the left mid-clavicular line. The aortic second sound was accentuated. No murmurs were heard. Breath sounds were diminished at both lung bases. The abdomen was normal.

The nervous system examination showed a right hemiparesis, already rapidly receding.

The urine was normal. The chest X-ray showed opacification of both costophrenic angles, a heart of normal position and size, and marked erosion of the lower rib margins. The œsophagus was normal. The electrocardiogram showed signs of left ventricular hypertrophy. A heart catheterization was done and the data obtained were compatible with right heart failure, with slight increase in right ventricular, pulmonary artery, and pulmonary " wedge " pressures.

A *selective angiocardiography* (Fig. 3), with the catheter placed in the right ventricle, showed during the opacification of the aortic arch a single large vessel coming off from the arch and giving branches only for the neck. In the lateral position the plates showed the same aspect—a single large vessel, giving branches to the neck. Normal pyelograms were obtained at the same time.

* Aided by a grant from the " Conselho Nacional de Pesquizas."

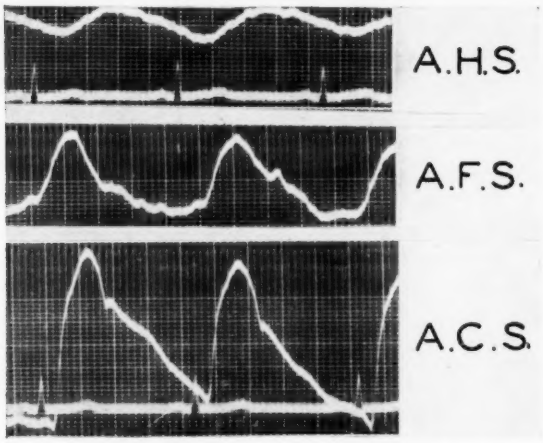

FIG. 1.—External recordings of the arterial pulses. A.H.S.—left humeral artery; A.F.S.—left femoral artery; A.C.S.—left carotid artery.

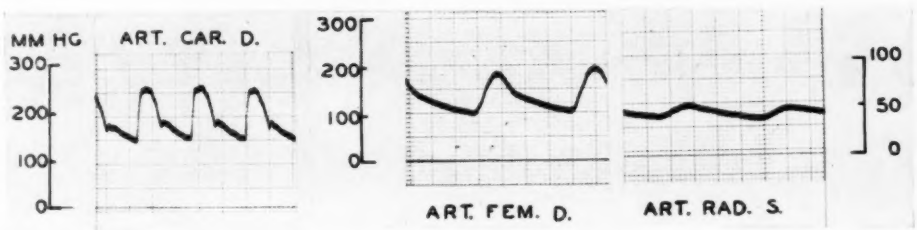

FIG. 2.—Intra-arterial recording of pressure.

Evolution. The signs of heart failure cleared up rapidly with digitoxin and the blood pressure came down to normal with reassurance and rauwolfia. Upon discharge, his speech and gait were almost normal.

Comments

The decrease or absence of pulses in both upper extremities has been reported in the arteritis of the aortic arch, comprising the so-called " pulseless disease", the outstanding symptoms of which are visual disturbances and syncopal attacks.

The absence of these last-mentioned symptoms and the normal pulses in both carotid arteries allowed us, on a clinical basis, to discard an arteritis of the aortic arch and to suspect an aortic arch anomaly. Also in favour of a congenital anomaly was the history of a " heart lesion " when 15 years old and the normality of the upper extremities as far as temperature, trophic state, and strength were concerned.

Although mentioned as a possibility (Giffin, 1939), no case of pulseless disease due to an aortic arch anomaly has yet been reported. Another interesting feature is the great increase of the intercostal circulation and the rib notching, listing one more ætiology for this well-known X-ray sign: in this case the circulation probably functions in the reverse direction from aorta to arm.

A case exactly similar to the above reported was seen at the Hospital dos Servidores do Estado, Rio de Janeiro, Brazil. A 46-year-old heavy labourer when examined was found with hypertension in the lower

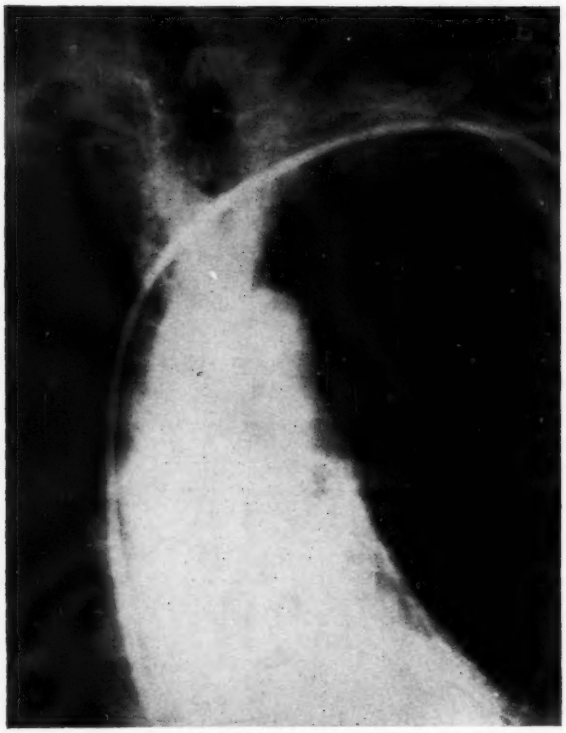

FIG. 3.—Angiocardiographic plate, showing the aortic arch opacified and a single large vessel coming off from it and giving branches only for the neck.

extremities (220/130), normal carotid pulsation, and extremely weak pulses in both arms. An aortography showed a single large vessel coming off from the aortic arch and giving branches only for the neck. A great increase in intercostal circulation was also seen in the aortography plates.

Summary

A 30-year-old patient is reported with absence of the pulse in both upper extremities. Pulses were normal in the leg and neck arteries. Intercostal collateral circulation and rib notching were observed. Angiocardiography showed a single large vessel coming off from the aortic arch and giving branches only for the neck.

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ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

Cardiovascular Innervation. G. A. G. MITCHELL, O.B.E., T.D., M.B., CH.M., D.SC. With a foreword by Sir Geoffrey Jefferson. Edinburgh and London: E. & S. Livingstone, Ltd., 1956. Pp. xii + 356. £2 15s.

This monograph on the innervation of the cardiovascular system is a notable addition that is likely to become the standard work of reference on this subject. The text, which is freely illustrated, is based largely on the author's own studies, by dissection and microscopy, of the anatomy of the autonomous nervous system in man and there is a comprehensive survey of the literature and of the historical aspects of the subject. This is a book on applied anatomy and the author has used the results of physiological, pathological, and clinical studies to elucidate the function of the autonomous fibres. The chapter on the innervation of vascular structures in the thorax gives an excellent description of the innervation of the coronary vessels which will be of interest to the clinician and the account of the nerve supply of the pulmonary vascular bed is of importance to those engaged in physiological studies on patients with heart disease.

Graham Hayward

A Post-myocardial-infarction Syndrome. Preliminary Report of a Complication Resembling Idiopathic, Recurrent, Benign Pericarditis. W. DRESSLER. *J. Amer. med. Ass.*, **160**, 1379–1383, April 21, 1956.

The author describes an unusual syndrome resembling benign pericarditis or the "post-commissurotomy syndrome", following a myocardial infarction. In 8 of the 10 cases a pericardial friction rub developed between the 3rd and the 24th days of the illness, persisted for a week or more, and in some cases recurred over a period of weeks. In 7 of the patients there was radiological evidence of pleural effusion, which was aspirated in 3 cases. Fever was prolonged after the initial infarction in 6 cases, in 2 a second rise of temperature occurred on the 9th and 15th days respectively, while in one case 8 weeks elapsed between the infarction and the onset of renewed fever. Pain, commonly of a pleuro-pericardial nature, was with fever the most consistent symptom and was felt at various sites, including the chest, jaw, arms, shoulders, and upper abdomen. A leucocytosis of as much as 35,000 cells per c.mm. occurred in 7 cases. The syndrome ran a prolonged course and showed a marked tendency to recur. Cortisone was found to terminate the fever and pain and to shorten the course of the syndrome. A warning is given that anticoagulant therapy is dangerous and is therefore contraindicated.

C. Bruce Perry

A Correlative Study of Valvular Morphology and Clinical Results in Aortic Commissurotomy. R. S. LITWAK, J. F. URICCHIO, and W. LIKOFF. *New Engl. J. Med.*, **254**, 781–786, April 26, 1956.

The authors have correlated some of the anatomical appearances noted at transaortic valvotomy with the late results in 40 patients (34 male and 6 female, aged 20 to 60 years) subjected to this operation. They found that the degree of calcification of the valve increased with advancing years, whereas limitation of mobility did not. Calcification was present to a greater or lesser extent in 35 (87%) of the patients and impairment of mobility in 28 (70%). Fusion of all three commissures was present in 30 (79%) of the patients, and in just under half (16 (42%) of 38 patients) the area of the aortic orifice was estimated as less than 0·5 sq. cm.

Valvotomy increased the opening in 24 cases (68·5%) to a size greater than 1·6 sq. cm., this figure being taken arbitrarily to represent an adequate anatomical result. Although generally the less the degree of calcification of the leaflets, the better is the chance of a satisfactory operation, nevertheless even in those with this complication an adequate split was achieved in 12 (52%) of those benefited.

Four of the patients died at operation and 7 died later, mostly of infective endocarditis. Of the 29 survivors, 23 were improved. As the authors point out, the dominant factor influencing the results was mobility of the valve, and so long as any mobility remained there was a possibility of improvement despite the presence of calcification.

J. R. Belcher

Bodily Development in Congenital Heart Disease. (Zur Frage der körperlichen Entwicklung bei angeborenen Herzfehlern.) A. SCHAEDE, H. LOTZKES, and H. H. HILGER. *Arch. KreislForsch.*, **24**, 1–26, June, 1956.

In an investigation carried out at the University Medical Clinic, Bonn, 750 young patients with congenital heart disease were seen between 1948 and 1953, of whom 576 who had been examined by means of angiocardiography and cardiac catheterization were further studied with regard to their subsequent bodily development as shown by body weight and height. They were classified into three groups: (1) those with no shunt (41 cases), (2) those with left-to-right shunt (117 cases), and (3) those with right-to-left shunt (418 cases), Group 3 being further subdivided according to (*a*) the severity of cyanosis and anæmia and (*b*) the pulmonary blood flow.

It was found that in all these patients bodily development was grossly reduced, weight being more affected than height.

D. Goldman

Surgery of the Heart. CHARLES P. BAILEY, M.D., M.Sc., L.L.D., F.A.C.S., F.C.C.P., F.I.C.S. London: Henry Kimpton. 1955. Pp. 1062. £9.

This book is a most important contribution to cardiac surgery and its large size reflects the rapid development and increasing scope of this method of treatment. The author has made notable contributions to the surgery of mitral valve disease and the section on this subject which occupies nearly a quarter of the volume is outstanding. The chapter on congenital heart disease reflects accurately the position when the book was written, but in a subsequent edition considerable revision of the treatment of septal defects and the practice of open heart surgery will need to be made. There is too much rather elementary cardiology included and its omission would decrease the size of the book without lessening its value. The selection of cases for the various forms of surgery is viewed largely from the point of view of the cardiac surgeon and a cardiologist would in many cases favour a more conservative approach to this problem, particularly at the present time when the value of the various operations described remains to be proved. The book is freely illustrated and can be strongly recommended.

Graham Hayward

Electric Instability of the Heart. The Concept of the Current of Oxygen Differential in Coronary Artery Disease. B. L. BROFMAN, D. S. LEIGHNINGER, and C. S. BECK. *Circulation (N.Y.)*, **13**, 161–177, Feb., 1956.

In only a small proportion of cases of coronary disease can death be attributed to the degree of myocardial destruction. The authors suggest that in other fatal cases there is a disorder of cardiac mechanism, and that possibly abnormal impulses (an "injury current") originating from the area of ischæmic myocardium give rise to ventricular fibrillation. They then describe experiments designed to study the manner in which an area of ischæmic myocardium may give rise to an injury current. In these the hearts of anæsthetized dogs were exposed, and areas of local myocardial ischæmia were produced by ligation of the coronary vessels.

It was found that in normally oxygenated hearts and hearts uniformly anoxic throughout there was no variation in the resting electric potentials and spontaneous ventricular fibrillation did not occur. However, when an area of myocardium was rendered ischæmic an injury current was produced, rendering the heart electrically unstable, so that the coordinating mechanism was upset. It was noted that this was associated with a difference of oxygen potential at the junction of normal and ischæmic myocardium. Moreover, it was shown that the uniformly anoxic heart was also electrically stable, but if an area was perfused with oxygenated blood a difference of oxygen potential arose at the border of this area and electric instability again developed, with the danger of ventricular fibrillation. The authors suggest that electrical instability of the myocardium due to unequal coronary blood flow may be responsible for the majority of deaths in patients with coronary disease.

H. E. Holling

The Effect of Prolonged Adherence to a Salt-free Diet on Life Expectancy in Essential Hypertension. H. SARRE, W. KAMPMANN, and G. SCHMIDT. *Klin. Wschr.*, **34**, 509–511, May 15, 1956.

In this paper from the University Medical Clinic, Freiburg-im-Breisgau, are reported the results of a 9-year follow-up study of 45 patients with essential hypertension who had been treated for a number of years with Volhard's salt-free diet under supervision of the staff of Volhard's own clinic. Proof of adherence to the diet was obtained by estimation of the urinary chloride excretion. A group consisting of 45 patients who had failed to adhere to the diet served as a control, the two groups being comparable in respect of the severity of the hypertension and of its complications; 30 patients in each group had a diastolic pressure of over 120 mm. Hg when first seen, while 15 patients in the control group and 16 in the treatment group had some degree of cardiac failure. [Unfortunately no mention is made of the age and sex distribution.]

It was shown that the difference in the expectation of life between the two groups was statistically significant for the first 3 years of treatment, 20 patients from the control group, compared with 9 from the treatment group, having died during this period. In the succeeding years, however, the mortality in the treatment group exceeded that among the controls, so that at the end of the 9-year period the number of survivors from each group was almost identical, namely, 11 in the control group and 12 in the treatment group. Analysis of the cause of death showed a marked similarity between the groups.

H. F. Reichenfeld

Amnion Implantation in Peripheral Vascular Disease. E. TROENSEGAARD-HANSEN. *Brit. med. J.*, **2**, 262–268, Aug. 4, 1956.

In this paper from the Charing Cross Hospital, London, the author reports the treatment of a series of 40 cases of intermittent claudication, by the implantation of human amnion into the thigh. This method of treatment was suggested by a chance observation that amnioplasty carried out for the treatment of gravitational ulcers had a beneficial effect on intermittent claudication. The patients, all of whom were men, ranged in age from 36 to 89, the average age being 60. Symptoms had been present for 6 months or more in all but 7 cases.

Exercise tolerance was increased in 7, and intermittent claudication disappeared in 29 cases, even on severe exercise, the follow-up period ranging from 8 months to 3 years. Clinical improvement was accompanied by a return of rate of disappearance of radioactive sodium to normal and improved performance in the ergometer tests. In 7 cases the dorsalis pedis pulse returned, while in 14 cases there was a marked increase in the oscillometer readings, though good results were not confined to these cases. In the skin temperature there was an immediate postoperative rise, followed after a month by a fall, which, however, was not accompanied by a recurrence of symptoms. The possible mode of action of amnion implants is discussed and an illustrative case history is reported in some detail.

H. F. Reichenfeld

Mecamylamine, a New, Orally Effective, Hypotensive Agent. Experimental and Clinical Evaluation. E. D. FREIS and I. M. WILSON. *A.M.A. Arch. intern. Med.*, **97**, 551–561, May, 1956.

Mecamylamine, a readily-absorbed ganglion-blocking agent, was tried in the treatment of hypertension.

Mecamylamine was given by mouth in an average daily dose of 29 mg. (range 3 to 90 mg.) for periods of 4 weeks to 4 months to 36 patients with moderately severe or severe hypertension. Satisfactory reduction in blood pressure was obtained in all cases, and in some instances improvement in the optic fundi, heart size, electrocardiogram, and renal function. Tolerance to the drug was absent or slight. The treatment of 4 patients had to be stopped because of side-effects. Almost all patients complained of constipation during treatment; other side-effects experienced by about a quarter of the patients included postural faintness, disturbances of accommodation, dry mouth, difficulty in micturition, and impotence.

Of 19 hypertensive patients given mecamylamine by mouth after receiving pentolinium tartrate by mouth for 6 months or longer, 14 preferred the former drug because of its more uniform hypotensive action.

Bernard Isaacs

Effect of Molar Sodium Lactate in Increasing Cardiac Rhythmicity. Clinical and Experimental Study of Its Use in the Treatment of Patients with Slow Heart Rates, Stokes-Adams Syndrome, and Episodes of Cardiac Arrest. S. BELLET, F. WASSERMAN, and J. I. BRODY. *J. Amer. med. Ass.*, **160**, 1293–1298, April 14, 1956.

The authors, from the General Hospital and the Graduate Hospital of the University of Pennsylvania, Philadelphia, describe the effect of intravenous and intracardiac injections of molar sodium lactate on 5 healthy controls and 41 patients with a slow heart rate. In 3 with sinus bradycardia there was an increase in heart rate of 50 to 70 per cent above control values during the intravenous infusion of 100 to 160 ml. of molar sodium lactate over 10 to 15 minutes. The same dose given by the same route increased the heart rate in 5 out of 6 patients with partial A-V block and 10 out of 12 with complete A-V block. From a study of 4 cases in which there were Stokes-Adams seizures the authors suggest that the prompt intravenous administration of 20 to 80 ml. of this preparation over a period of 2 minutes, followed by an intravenous infusion at the rate of 1 ml. per minute for 6 to 12 hours, may suffice to prevent subsequent attacks. In 12 cases of terminal cardiac arrest the heart beat was restored by intravenous or intracardiac injection within 2 minutes of molar sodium lactate, and was maintained, with associated artificial respiration, for as long as 9 hours by continuous infusion.

There were few toxic effects from the sodium lactate injections. Pulmonary œdema was not encountered. It is considered that the mode of action of the lactate is related to the alkalosis produced by the injection, and that the lactate is metabolized.

W. J. H. Butterfield

The Surgical Treatment of Aortic Stenosis. C. P. BAILEY, H. E. BOLTON, H. T. NICHOLS, W. L. JAMISON, and R. S. LITWAK. *J. thorac. Surg.*, **31**, 375–437, April, 1956.

[This article is probably the most comprehensive and detailed account of the surgical treatment of aortic stenosis that has been written. Moreover, the authors do not confine themselves to surgery but give an extensive survey of the ætiology and hæmodynamics of the condition.]

In this review, from Hahnemann Medical College and the Bailey Thoracic Clinic, Philadelphia, of the surgical treatment of aortic stenosis, three main types are distinguished. (1) A congenital form, in which the valves are often bicuspid and post-stenotic dilatation is usually present. (2) Arteriosclerotic stenosis. (3) Rheumatic aortic stenosis. The critical point at which there is difficulty in ejection of blood from the ventricle occurs when the area of the orifice is reduced by 75 to 90 per cent. The period of ejection is then unduly prolonged, as may be shown by a study of pressure curves. The blood supply to the heart muscle is also diminished as a result of the lower systolic pressure at the root of the aorta, thus accounting for the anginal symptoms from which many patients suffer.

The surgical approach to the aortic valve may be through the left ventricular wall or through the aorta. The transventricular approach in 68 cases of uncomplicated aortic stenosis gave an operative mortality of 28 per cent. In 87 cases of combined mitral and aortic stenosis the mortality was 18 per cent. The causes of operative death are principally ventricular fibrillation, heart arrest, and hæmorrhage. The transaortic approach is now considered to be safer. The mortality by this procedure (15%) is appreciably lower than that by the transventricular route.

The authors discuss the selection of patients and the techniques of valvotomy in detail. The authors' results suggest that more than 80 per cent of the survivors show improvement over a follow-up period of 1 to 3 years.

T. Holmes Sellors

Cardiocirculatory Studies in Pulsus Alternans of the Systemic and Pulmonary Circulations. M. I. FERRER, R. M. HARVEY, A. COURNAND, and D. W. RICHARDS. *Circulation (N.Y.)*, **14**, 163–174, Aug., 1956.

Studies carried out in 21 patients have indicated that alternation of the pulse pressure in man can occur independently in either the greater or the lesser circulation without appearing in the other. Even when bilateral alternation exists, this cyclic variation may disappear in one circulation while persisting in the other. Although pulmonary or systemic hypertension was frequently associated with pulmonary and systemic alternans respectively, hypertension was not invariably present. Furthermore, changes in lesser or greater circulation pressures bore no consistent relationship to the appearance or disappearance of pulsus alternans. Mechanisms responsible for pulsus alternans, in particular variations in stroke volume and vascular pressures, were considered, but no single explanation satisfied the facts revealed in this study.—[Authors' summary.]

The Body Fluids; Basic Physiology and Practical Therapeutics. J. RUSSELL ELKINGTON, M.D., and T. S. DANOWSKI, M.D. Pp. 626 with 175 illustrations. London: Baillière, Tindall and Cox. Price 80*s*.

The first parts of this monograph describe the basic physiology and biochemistry of the body fluids and the causes and effects of changes in the water and electrolytes of the body that may be encountered clinically. There is a full description of the changes in various disease entities such as renal failure, congestive heart failure, cirrhosis, and endocrine disorders, and a final section on practical therapeutics. The rapid growth of knowledge in this particular field and the complicated nature of the changes that may occur emphasize the need for such a monograph which enables the clinician to make the best use of modern biochemical investigations in the diagnosis and treatment of patients. *Graham Hayward*

Cardiac Septal Defects. I. Ventricular Septal Defect. Analysis of One Hundred Cases Studied during Life. D. F. DOWNING and H. GOLDBERG. *Dis. Chest*, **29**, 475–491, May, 1956. 2 figs., 6 refs.

The authors believe that most textbook descriptions of ventricular septal defects wrongly convey the impression that these lesions are relatively benign. They have therefore analysed the records of 100 patients (50 of each sex) with such a lesion seen at Hahnemann Medical College Hospital and the Bailey Thoracic Clinic, Philadelphia, of whom 76 were under 15 years of age. All the patients were studied by means of cardiac catheterization, and in 22 cases angiocardiography or thoracic aortography was carried out in addition.

Symptoms possibly of cardiac origin were present in 89 patients, the chief being fatigue in 72, dyspnœa in 71, and cyanosis in 39, while cardiac failure had occurred in 22; rarer symptoms were chest pain, chronic cough, paroxysmal tachycardia, hæmoptysis, and syncope. Radiologically, the great majority of patients showed right ventricular enlargement with exaggeration of the hilar and peripheral pulmonary vessels. Evidence of right ventricular hypertrophy was found in 59 per cent of the electrocardiograms. Cardiac catheterization revealed a rise in the oxygen content of the blood on passing from right auricle to ventricle in 90 patients, and 34 were thought to have had a right-to-left shunt. Seventy-two patients were found to have pulmonary hypertension.

As in other conditions causing a left-to-right shunt, the pulmonary vascular resistance increases. Thus there is a progressive rise of right heart pressure; when this exceeds the systemic pressure a right-to-left shunt with cyanosis develops. In this way the features of Eisenmenger's complex appear. The authors do not consider this complex to be a separate entity; their findings suggest that in all cases the aorta can be "aligned" with the left ventricle, and that true overriding in this condition does not occur. In conclusion they emphasize that ventricular septal defect is a serious lesion, which causes symptoms in the majority of those affected and cardiac failure in a large number. *F. Starer*

Diseases of the Heart and Circulation. PAUL WOOD. 2nd edition, revised and enlarged. Eyre & Spottiswoode (Publishers) Ltd. Pp. 1005. Price 5 gns.

The high reputation that the first edition of this book published in 1950, acquired will be enhanced by the new edition which has been extensively revised and includes much new material and many new illustrations. The striking advances that have been made in the investigation and treatment of congenital heart disease and acquired valvular disease have resulted in a considerable expansion in the chapters on these subjects, which now occupy over a quarter of the book. Although, as the author states in the preface, there may be over-emphasis on this new work, the result has been to produce one of the best contemporary accounts of the use of modern methods of investigation in cardiology. Throughout the book there is emphasis on the importance of clinical methods of examination and the author shows how the results of special methods of investigation have been used to increase the accuracy of clinical diagnosis and to influence treatment. The style of writing is incisive and the author's own views are stated clearly but without dogmatism. This book can be highly recommended.
Graham Hayward

Le Systeme "Pompe-Oxygenateur" de Lillehei-Dewall: Coeur-Poumon artificiel pour chirurgie cardiaque sous vision directe. CLAUDE LENFANT. Nouvelle Editions Publicitaires. Paris. 55 figures. 270 pages.

This monograph describes the experimental work done by the author and his colleagues at the Centre Chirurgical Mari-Lannelongue in preparation for using the apparatus for operations on patients; it consists of three parts.

(1) *The Appratus.* Each of the constituents of this is described in detail and the authors find that with it an arterial oxygen saturation of nearly 100 per cent can be maintained. They describe three modifications they have made to obtain an adequate oxygen supply for operations on animals of more than 20 kg.—additional apparatus for filtration, enlargement of the oxygenator circuit by increasing the mixing tubing and the spural, and a method of recovering the coronary blood, so that this was not wasted. With these they were able to obtain a supply of from 1800 to 2000 ml. of oxygen a minute.

(2) *The Operations.* Seventy operations on animals, mostly dogs, are described, and the final methods that were reached for using this for surgical operations on men. In favourable conditions they obtained a survival rate of 90 per cent and thought that deaths were generally due to hazards of the operation rather than faults of the apparatus.

(3) The third part is devoted to studying the physiological state during the use of the apparatus. They found that conditions generally were satisfactory with the use of 35 ml. per kg. per minute of oxygen though this could be increased up to 58 ml. per kg. and that this was compatible with the animal's recovery in good condition after a period of thirty minutes.

This monograph contains so much important detail that it should be consulted in the original by those interested. *Maurice Campbell*

Dilatation of the Pulmonary Artery in Pulmonary Stenosis. F. S. P. VAN BUCHEM. *Circulation (N.Y.)*, **13**, 719–724, May, 1956.

An attempt was made at the University of Groningen to correlate the diameter of the pulmonary artery (obtained at angiography with the patient in the oblique position) and the systolic pressure difference between the right ventricle and pulmonary artery in 20 cases of simple pulmonary valvular stenosis. Stenosis was mild in the majority, the pressure difference being under 30 mm. Hg in 10, 40 to 50 mm. Hg in 6, and over 100 mm. Hg in 4. The diameter of the pulmonary artery, normally 22 to 33 mm. by this method, ranged from 30 to 75 mm., and evidently bore no relation to the severity of the stenosis or to the age of the patient. In 6 cases of "idiopathic dilatation of the pulmonary artery" in which pulmonary stenosis had been excluded by cardiac catheterization the appearance of the dilated artery resembled that found in cases of pulmonary stenosis and its diameter ranged from 39 to 49 mm. From this evidence the author concludes that dilatation of the pulmonary artery is probably a primary condition, and is not merely secondary to the valvular stenosis.

J. A. Cosh

Pulmonary Valvular Stenosis with Intact Ventricular Septum. Results of the Brock Type Valvulotomy. C. W. LILLEHEI, P. WINCHELL, P. ADAMS, I. BARONOFSKY, F. ADAMS, and R. L. VARCO. *Amer. J. Med.*, **20**, 756–759, May, 1956.

The authors report the findings on re-examination after operation of 20 out of 43 patients subjected to pulmonary valvotomy by the Brock technique, the average interval since operation being 15 months. The auscultatory findings changed very little. In a small number of cases there was a diastolic murmur consistent with pulmonary incompetence. The most significant alteration occurred in the right ventricular pressure. For the whole group the average reading was 116 mm. Hg before operation and 56 mm. Hg afterwards; when the 5 cases in which there was no significant alteration were excluded the figures were 123 and 43 mm. Hg respectively. Especially gratifying was the response in the cyanotic group (7 patients), in whom the fall in the hæmoglobin level and the increase in arterial oxygen saturation reflected the significant alteration produced in the right ventricular pressure.

R. G. Rushworth

Hæmatogenous Brain Abscess in Cyanotic Congenital Heart Disease. E. J. NEWTON. *Quart. J. Med.*, **25**, 201–220, April, 1956.

Over the 10-year period 1944–53 69 patients with solitary hæmatogenous brain abscess have been treated at the United Birmingham Hospitals; of these, 7 had congenital heart disease of the cyanotic variety, that is, with a central venous-arterial shunt. These cases were specially investigated, are described in detail, and discussed together with 72 previously reported cases, the salient features of which are given in a table.

In most of these 79 cases the abscess arose without any underlying septicæmia or pyæmia and in the absence of subacute bacterial endocarditis, nor could it be attributed to any thoracic cause such as lung abscess, empyema, or bronchiectasis, or to infection of the mastoid or paranasal air sinuses—in short, to none of the usual causes of brain abscess. It appears, therefore, that a central venous-arterial shunt predisposes to hæmatogenous brain abscess, possibly on account of the partial by-passing of the pulmonary capillaries, where it is probable that many blood-borne bacteria are filtered out of the circulation and dealt with effectively in the normal person during the course of a transient bacteriæmia. The author stresses the importance of being aware of the tendency for brain abscess formation in cases of cardiac malformation of this type; in cases with an arterio-venous shunt there appears to be no special association with brain abscess.

Of 75 of the 79 cases reviewed, 40 were in males and 35 in females, so that the sex distribution was approximately equal. The patients' ages ranged from 3 to 57 years, average 16·3 years, the highest incidence (23 cases) being in the age group 5–9. The most frequent type of cardiac malformation was Fallot's tetralogy (23 certain cases and 12 probable cases). There appeared to be no special site of predilection for the abscess in the brain. The diagnosis of the condition lies largely in being aware of its possibility; the most prominent symptom in these cases was prolonged headache. Treatment, by aspiration through a burr-hole and systemic administration and local injection of an antibiotic, was on orthodox lines.

G. S. Crockett

Coronary Arteriosclerotic Heart Disease in the Younger Age Group: Its Greater Frequency in This Group among an Increasingly Older Necropsy Population. O. SAPHIR, L. OHRINGER, and H. SILVERSTONE. *Amer. J. med. Sci.*, **231**, 494–501, May, 1956.

Having observed in recent years an apparent increase in the incidence of arteriosclerotic heart disease (A.H.D.) in the younger age groups, the authors studied the necropsy records at the Michael Reese Hospital, Chicago, covering a period of 34 years. All cases of coronary arteriosclerosis or atheromatosis with or without myocardial fibrosis or infarction in patients over the age of 20 were included, except those in which there were minimal changes. The necropsy records for 3 different periods, 1920–39, 1940–9, and 1950–3, were studied, the incidence of A.H.D. being as follows: 31 per cent of 2696 necropsies in 1920–39; 32 per cent of 2764 necropsies in 1940–9; and 29 per cent of 1572 necropsies in 1950–3.

Altogether 2165 patients had A.H.D., 1403 being males. The proportion of these patients under the age of 50 rose from 7·3 per cent in 1920–39 to 12·2 per cent and 11·5 per cent in 1940–9 and 1950–3 respectively, the greatest increase being in patients aged 40 to 49. Nevertheless, the total number of cases of A.H.D. found at all necropsies did not rise, and the total number of necropsies performed on patients under the age of 50 fell considerably. The authors therefore consider that these figures indicate a significant increase in the number of cases of A.H.D. in the younger age groups; in their view this increase may be related to factors other than diet.

Francis Page

Diseases of the Heart. CHARLES K. FRIEDBERG, M.D. Second edition. Pp. 1161. London: W. B. Saunders & Company Ltd. Price £6 6*s*.

The new edition of Friedberg's textbook has been reset so that although the length of the text has been considerably increased the size is only slightly increased. Three new chapters on graphic methods of examination have been added and the extensive revision of all sections of the book includes accounts of the recent work on direct vision cardiac surgery and the selection of patients for surgical treatment. The scope of the book is encyclopædic and it is a considerable achievement for a single author to have presented such a complete account of modern developments in all aspects of cardiology. A notable feature is the bibliography which is unusually extensive and complete. *Graham Hayward*

The Influence of Mitral Regurgitation on the Results of Mitral Valvotomy. J. R. BELCHER. *Lancet*, **2**, 7–11, July 7, 1956.

The results of mitral valvotomy in 52 patients with mitral incompetence were compared with those obtained in 100 patients operated on for pure stenosis. The state of the valve was fully assessed with the finger before operation. The degree of regurgitation was noted and the cases classified in 4 grades, while the degree of stenosis was recorded on a 5-point scale. On the basis of mobility the valves were classified as hypermobile, diaphragmatic, or immobile. After valvotomy the degree of split was assessed and the degree of regurgitation reassessed.

In cases in which a diaphragmatic valve was found the results of valvotomy were fairly good, even when incompetence was dominant; the degree of regurgitation was increased by the operation in relatively few instances. On the other hand the results in cases of hypermobile and immobile valves were poor, and the author suggests that if the presence of these valves can be confidently diagnosed surgery should not be undertaken. Traumatic mitral incompetence was caused by valvotomy in 10 cases, but this had little influence on immediate results, the dominant factor being the efficacy of the split. The severity of the postoperative incompetence had more influence on the late results.

There were 7 operative deaths and one late death among the 100 patients with pure stenosis and 3 operative and 6 late deaths among those with incompetence (most of the deaths in the latter group occurred in patients with hypermobile and immobile valves).

The mechanism of production of the clinical signs and the differential diagnosis of the three types of valve are discussed. It is concluded that the clinical diagnosis of the anatomical type of valve may be possible, that valve mobility plays a dominant part in operability, and that commissurotomy is all that is necessary where a diaphragmatic valve is found; in cases in which diagnosis of one of the other types of valve can be made with certainty surgery should be withheld until suitable methods of treatment have been developed.

F. J. Sambrook Gowar

The Serum Lipids in Human Atherosclerosis. An Interim Report. J. C. PATERSON, B. R. CORNISH, and E. C. ARMSTRONG. *Circulation* (*N.Y.*), **13**, 224–234, Feb., 1956.

This is an interim report on a study of serum lipids in relation to the progression of atherosclerosis which is being made on 800 patients permanently confined to the Westminster Hospital, Department of Veterans' Affairs, Western Ontario, 700 of them being psychotic and the remaining 100 being elderly and in need of domiciliary care. Since April, 1953, specimens of blood have been obtained at yearly intervals from each patient.

The findings are now reported in the first 50 fatalities in the series, the mean antemortem serum cholesterol and phospholipid values and those of four classes of lipoproteins (S_f 0–12, 12–20, 20–100, and 100–400) being compared statistically with the degree of atherosclerosis present at necropsy. This last was determined in segments of the coronary arteries, the basilar artery and circle of Willis, the abdominal aorta, and the left femoral artery, the degree of atherosclerosis being graded in each case as "severe," "moderate," or "slight" according to each of 6 different indices—crude morphological grading, thickness of the largest plaque, total content and concentration of lipid, and total content and concentration of calcium. Thus the relationship of each of the 6 different measures of atherosclerosis in 4 types of artery to the mean antemortem level of 6 different lipids in the serum could be determined. Almost all the 50 subjects were in the 6th to 9th decade, the age distribution in the whole series being 40 to 90 years or more.

In the analysis of the findings in these first 50 cases only 4 of the 138 sets of comparisons showed a significant relationship, namely, an increase in the serum cholesterol: phospholipid (C:P) ratio and an increased concentration of S_f 0–12 lipoproteins in the serum in association with severe coronary sclerosis, an increased serum concentration of S_f 0–12 lipoproteins in association with severe aortic sclerosis and an increased serum C:P ratio in association with severe femoral sclerosis. Even these associations were not consistent. There was no significant elevation of the serum level of any of the lipids or lipoproteins in any of the cases with gross clinical manifestations of atherosclerosis such as coronary thrombosis. The serum cholesterol, phospholipid, and S_f 0–12 lipoprotein values estimated serially were remarkably constant in each case, but the values for the other lipoproteins were more variable. The severity of atherosclerosis in different arteries in the same individual varied widely. *Robert de Mowbray*

WILLIAM HARVEY

April 1, 1578—June 3, 1657

A Tercentenary Congress to commemorate William Harvey was organized by the Harveian Society of London with the help of the Royal College of Physicians and other Societies and was held at the Royal College of Surgeons, London, from June 3 to June 7, 1957. It was concluded at Folkestone two days later with a memorable address by the President, Dickson Wright, before the statue of Harvey, which looks across the Channel from the cliffs where he played as a boy. The Congress included some historical papers as well as many dealing with our present knowledge of the circulation, excellent scientific exhibitions, and films and colour television. It need not be recorded in detail, for the Committee intend to publish the Proceedings.

A special meeting of the British Cardiac Society was held as part of the Congress on Thursday, June 6, and abstracts of this meeting appear as usual in the Proceedings. We are glad to print this pertinent historical paper by Morgan Jones.

There seems no doubt that William Harvey was greatly influenced by the four years he spent in Padua from 1598 to 1602. At this University there was a freedom of thought and of expression that was hardly found elsewhere at the time. Harvey was a pupil of Fabricius (1537–1619) who followed the great teachers Vesalius (1514–1564) and Fallopius (1523–1563)—earlier occupants of the same Chair.

If Harvey is to be regarded as the father of modern experimental physiology and medicine, the publication of *De Fabrica Humani Corporis* by Vesalius in 1543 marked the beginning of modern anatomy. Harvey has acknowledged the influence of Fabricius, who had published beautiful descriptions of the valves of the veins but was still too much under the influence of Galen to make the deductions that Harvey did.

There was some glimmering of knowledge of the circulation through the lung before this. Servetus (1511–1553) in *Restitutio Christianismi* (1553), most copies of which were burnt with him at the stake, had surmized the existence of the pulmonary circulation; Columbus (1516–1559), perhaps following Servetus, taught this at Padua; and the philosophical physician Caesalpinus (1519–1603) included a rather fuller description of it in his *Questiones peripateticae* (1571); but none of these authors brought forward any evidence to support their rather speculative views or had any real influence on contemporary thought.

As Morgan Jones points out, we owe a debt to Harvey for his clear demonstration of the experimental method, as well as for his discovery of the circulation. Those who have seen the beautiful film originally produced by Sir Thomas Lewis and Sir Henry Dale for the Royal College of Physicians in 1928, and now remade by Sir Henry Dale in colour, cannot fail to realize the wonderful simplicity of his experiments and the decisiveness of the deductions that he made from them.

DOGMA AND EXPERIMENT IN HARVEY'S TIME

BY

A. MORGAN JONES

A Lecture given in the History of Medicine Series at the University of Manchester, November 8, 1956

Although William Harvey is usually remembered for his discovery of the circulation of the blood, this is not the only reason for choosing him as the pivot of this lecture: it is also his attitude to truth and knowledge which well exemplifies the spirit of his age, and this spirit is more important than any single discovery, however significant. Harvey was born towards the end of the 16th century (in 1578) and died at the age of 79 in 1657. During the 16th and 17th centuries there were great changes in outlook which transformed the whole complicated structure of mediæval thought to modernism. To appreciate the nature of this change and the spirit of the times in which Harvey lived, it is necessary to develop at least an outline picture of the attitude of mediæval man to truth and knowledge for these ideas existed into Harvey's time and in some respects well beyond it.

Mediæval Scholasticism

At the beginning of the 12th century Christian beliefs were dominated by the Early Fathers of the Church, such as St. Augustine. But during the 12th century there came a revival of intellectual and spiritual curiosity which was influenced by a renewed interest in the rational philosophy of Aristotle. This renaissance of thought threatened the authority of the Church for it began to set reason against faith. In this crisis, a 13th century Dominican friar, Thomas Aquinas, came to the rescue and, by reconciling the rival claims of faith and reason in a great ideological synthesis, maintained the supremacy of the Church and harmonized its beliefs with the philosophy of Aristotle. In his system the Church was still the basis of all—it was established by God and endowed with a head in the person of Peter whose authority was transmitted from age to age through each successive Pope. Its function was to guide man, by its teaching and worship, to his eternal home. Upon these premises Thomas Aquinas erected a logical ideology which covered every aspect of human life. All knowledge and all values were within his province, and he gave answers to all human problems: he was concerned with vitally important things—with conduct and duty, with law and government, with morals and marriage and, of course, in the end with the soul and salvation. Every point is rationally argued in the terms of formal logic. Thomas Aquinas was not ignorant of the possibility of experiment, nor of the value of experience, but to simplify his immense task he deliberately chose to base his work on authority, and to ignore experimental evidence and deduction from observed facts. Although his views are still the subject of controversy, he achieved a great code of human values and conduct, abounding in common sense. With good reason Pope Leo XIII proclaimed it in 1879 the official philosophy of the Roman Catholic Church, though it had for long been unofficially accepted.

The sort of truth that interested Thomas Aquinas was essentially different from the truth that science seeks. His world " presented man as shut up in himself—surrounded by self-conditioned ideas or divine revelations " (Mumford). The external natural world was of interest only in relation to man's destiny. He was not interested in " how " natural phenomena take place, which is the concern of science, but in " why " they exist. This was the natural outcome of his attitude, for he believed that knowledge was stationary—not progressive—so he sought for understanding and not new knowledge. Indeed he feared that any attempt to discover new facts might only

mislead. When Galileo, in Harvey's time, showed that the milky way was composed of an enormous number of stars (and not meteors as Aristotle had declared) Francesco Sizi, a distinguished Florentine divine, refused to confirm this by looking through Galileo's telescope lest he deceive himself; for, Francesco argued, if Galileo saw what *could* not exist, there must be optical defects in his telescope.

In mediæval times there existed, side by side with the close-knit philosophy of Thomas Aquinas, a rich pattern of subjective fantasies, which made up the popular world-picture of the Middle Ages. Of these Lewis Mumford wrote in *The Condition of Man*—" The stars that interested mediæval man were not nature's stars, but the stars of astrological lore: stars that guided the Magi to Bethlehem or foretold one's luck in love or war. The four points of the compass were not just geographical directions: they pointed to a mystical arithmetic: there was a mysterious connection with the four elements, air, earth, water and fire; with the four rivers of paradise, with the four winds, with the four humours of the body, and with the four cardinal virtues of the soul. The four sciences of the Quadrivium [arithmetic, geometry, music, and astronomy] plus the three sciences of the Trivium [grammar, rhetoric, and logic] produced seven: both three and four, magical in themselves, had magical consequences: the seven planets, the seven virtues, the seven deadly sins, the seven tones of the Gregorian chant all exhibited this secret correspondence between thoughts and things. Even Thomas Aquinas pointed out at length the exquisite fitness of the seven sacraments, which corresponded to the seven ages of man."

Yet there was throughout the Middle Ages some conflict between the rich fantasy of inner thought and the daily experience of man. For this was an age of craftsmanship: the great mediæval cathedrals are alone sufficient witness of that. The craftsman, " in struggling with obdurate materials, melting and colouring glass, hammering iron, hewing stone, and beating copper, must have learnt that practical knowledge could be gained by experience, and prayer would work only if its efficacy was added to the intelligent manipulation of materials." This, Mumford writes, was the daily lesson of craftsmanship. It is perhaps because of the effect of manual skill upon thought that there was so much opposition to practical methods in medicine in the Middle Ages. It was this that was responsible for the unwillingness of anatomists to do their own dissection—a reluctance that generally existed until the 16th century. In the 12th century the University of Paris expelled physicians who worked with their hands. Students of medicine could not let blood or perform any sort of operation and both surgery and dentistry were in disrepute. Mumford believes that this separation of the hand and the mind, which existed for many centuries, has done mischief that still exacts a toll today. He wrote: " the glorified garage mechanic, the pompous faith healer, and the mental dissectionist who treats diseases, not human beings—all these are still witness to the ancient quarrel between the unhandy minds and the unminded hands of the 17th century." We have only to look around in our daily work to recognize that there is some truth in this. Indeed, until the last year or two the roll of our hospital medical board continued to give mediæval precedence to the " unhandy minds " over the " unminded hands."

But it would be a mistake to believe that mediæval dogma and logic did only harm in obstructing the development of experimental science. In *Science in the Modern World* Whitehead wrote " the habit of exact thought was implanted in the European mind by the long dominance of scholastic logic and scholastic divinity. The habit remained long after the philosophy had been repudiated, the priceless habit of looking for an exact point and of sticking to it when found. Galileo owes more to Aristotle than appears on the surface of his *Dialogues*: he owes to him his clear head and his analytic mind." And more than that, for mediævalism contributed to science an ineradicable belief that " every detailed occurrence can be correlated with its antecedents in a perfectly definite manner, exemplifying general principles. Without this belief the incredible labours of scientists would be without hope " (Whitehead).

This is the background of mediæval thought which exerted so great an influence upon men's minds into the time of Harvey: it was both the foundation upon which he had to build, and the prison from which he sought to escape.

England in the 16th Century

But what of the English social, political, and intellectual environment into which Harvey was born in the 20th year of Elizabeth's reign? I despair of trying to summarize in a few sentences the story of England in the 16th century; I know that I shall be forced into those broad generalizations that historians so rightly condemn, yet seem so unable to resist. So I may as well begin with one from the pen of a distinguished historian. In *Tudor England* Bindoff described the state of the country in 1558, when Mary died, as " politically bankrupt, spiritually impoverished, economically anarchic, and intellectually enervated." The scene was, in fact, still strewn with the debris of the great creative upheaval in the reign of Henry VIII.

For two centuries England celebrated November 17, for it was on this day in 1558 that Elizabeth, the last child of Henry VIII, became Queen at the age of 25. To her political genius and her judgment of men, the England of Harvey's early years owed a great deal. Under her prosperity slowly returned, and Elizabeth assisted recovery by wise measures. First she restored the coinage, surprisingly, it is said, at a profit to her Treasury. Then came the Statute of Artificers, a great code of labour, which laid down the universal obligation to work and enacted a period of seven years apprenticeship in the skilled trades, so raising the standard of workmanship and increasing the pool of labour. The problem of the poor she dealt with by laws governing the collection and distribution of relief. In this way, the State took over economic life from the Guilds and charity from the Church much as it had earlier taken over government from the feudal barons.

The social and political achievements of the 16th century are not very obviously connected with the extraordinary progress that was made in literature, art, architecture, and music, for this was a development of the Renaissance on the continent and, like Harvey's own work, owed much to Italian influence. With the English Renaissance came the poetry of Michael Drayton (1563–1631) and Edmund Spenser (1552–99), the drama of William Shakespeare (1564–1616) and Christopher Marlowe (1564–93), and the prose of Francis Bacon (1561–1626), Richard Hooker (1554–1600), and Walter Raleigh (1552?–1618), to mention only a few. In 1563 the first English book on architecture was published—John Shutes' *Chief Groundes of Architecture*—and the building of fine houses flourished as never before. English music achieved a contemporary reputation it has never since regained, though most of the composers of that time are now forgotten. Under Elizabeth the growth of prosperity and confidence in the future contributed to a new unity from which the spirit of a nation emerged—and with it came a willingness to adventure and an urge to explore new places. The exploits of Elizabethan seamen, such as Hawkins, Drake, Grenville, and Frobisher, have grown into legends. This adventurous spirit had a parallel in thought, for there was a greater willingness to turn outward from the inner philosophy of mediæval times to explore the secrets of nature, and a surer belief that new knowledge of significance could be gained by observation and experiment. But the regression of mediæval concepts was very slow and it was not until almost a century after Harvey's birth that Boyle in his *Sceptical Chymist* (published in 1661) challenged the mediæval idea that all physical objects were made of a combination of two or more of the elements earth, air, fire, and water. Nor did Francis Bacon, a distinguished Elizabethan, ever accept the early 16th century view of Copernicus that the earth rotated round the sun.

This was the English environment into which Harvey was born at Folkstone in 1578: a new spirit of exploration of things material and things of the mind was abroad, but the hold of mediæval ideas, although slackening, was still a power to be reckoned with.

Harvey's Education

At the age of 10, Harvey entered the Grammar School of Canterbury in the year in which the Spanish Armada was destroyed. Most of the grammar schools of the time had been founded to replace the educational facilities that had been destroyed by the dissolution of the monasteries after 1530. The teaching they gave was confined mainly to Latin, Greek, and Hebrew, the three languages necessary for biblical study and theological controversy. Harvey was certainly an able Latin scholar and it is said that Virgil was his favourite author. In 1593, at the age of 16, he obtained

a scholarship to Caius College, Cambridge, and took his B.A. degree in 1597. Harvey was fortunate in the time he went to Cambridge for between 1530 and 1560 Oxford and Cambridge went through a difficult time, their wealth and numbers being greatly reduced by the disappearance of the monks and friars after the dissolution of the monasteries and by the subsequent economic difficulties of the country. But in Elizabeth's reign a new and more secular Oxford and Cambridge grew up, much freer from mediævalism; many undergraduates were destined for lay careers and the most prominent men of the time had studied at Oxford or Cambridge. The college system was replacing hostelries and lodging houses and, although there were no official tutors, private contracts were made with Fellows on the master and apprentice basis. Unfortunately, the services given by Fellows often depended more upon the wealth of the parents than the ability of their offspring! But the Church still had great influence, and the Dons were compelled to take Holy Orders and to remain unmarried; attendance at College Chapel was enforced on all. Today universities are amongst the main sources of new ideas, but in Harvey's time they were strongholds of resistance against the unorthodox.

When Harvey left Cambridge and came to consider his medical education it was natural that he should think of Padua, for at that time its medical school justly enjoyed an unrivalled reputation, and many distinguished English physicians had studied there. At Padua, between 1598 and 1602, Harvey must have become familiar with current ideas upon the movement of the blood. Galen was still the paramount authority, and Harvey in his writings shows his deep, even exaggerated, respect for Galen's views. Galen believed that the portal venous system carried materials from the alimentary tract to the liver, where blood was formed and charged with natural spirits. In the hepatic veins the blood ebbed and flowed between the liver and the right ventricle. A little penetrated drop by drop through pores in the ventricular septum, to meet in the left ventricle air containing vital spirits drawn from the lungs by the pulmonary veins. The combination of the blood with vital spirits in the left ventricle led to the production of heat, and the function of the lungs was to dissipate this heat, hence the warmth of the expired air. The blood mixed with vital spirits was distributed to all parts of the body by the arterial system, in which the blood ebbed and flowed. The venous system was centred on the liver, which distributed blood not only to the right ventricle but also to the whole body by ebb and flow in the superior and inferior venæ cavæ. The venous blood, in addition to carrying natural spirits, served to remove waste products from the tissues, and these waste products were discharged from the right ventricle by the pulmonary artery to the lungs.

These ideas explained a great deal of the gross anatomy of the liver, of the portal and systemic venous systems, and of the heart, lungs, and arteries. They explained why the body was warm, why death occurred when breathing stopped, and why this led to coldness of the body. Galen's ideas were so closely knit into an anatomico-physiological concept, which provided explanations for almost all the known facts, that to alter them meant the abandonment of a whole system of physiology, and moreover, a system backed by centuries of authority, embraced by the all-pervading Church, and almost universally accepted by the mediæval world. To criticize it was an act of courage: to put something better in its place was a great achievement.

Amongst Harvey's predecessors it was those who did not accept the mediæval schism between hand and mind who blazed a trail towards the ultimate discovery of the circulation. Leonardo da Vinci (1452–1519) was the first to make accurate drawings of the human heart, its valves and its vessels. He showed the complete occlusion of the ventricles by the auriculo-ventricular valves and, by experiment on a living pig, demonstrated the active contraction of the heart muscle, in contradiction of the Galenical doctrine of passive dilatation. He did not conceive the idea of the circulation of the blood, but likened its flow to the rise and fall of the tide. Leonardo attempted to calculate the outflow of blood from the heart, though erroneously. But the quantitative approach he used was entirely new in his time, and it was subsequently adopted by Harvey in *De Motu Cordis*.

Vesalius (1514–64) when Professor of Anatomy at Padua, also did his own dissections and came to the conclusion that there was no visible way for blood to pass through the ventricular

septum. Since he worked within the grasp of the Italian Inquisition, he may not have cared to stress this refutation of Galen's views, and he suggested that the blood " sweated " through the septum. There is, however, some reason to believe that Vesalius committed himself much more strongly in his lectures at Padua than he ever did in writing.

Michael Serveto, born in Navarre, Spain, in 1511, was a theologian but he made a surprising contribution to the circulation in a book on theology (*De Restitutio*), in which he stated that the blood is driven from the right ventricle to the lungs " where it mingles with the inspired air and is cleansed from its fumes " eventually being " drawn into the left ventricle during its expansion." In 1553, the year in which this was published, Serveto was burnt alive for heresy in Geneva, then a small Protestant republic in which Calvin was virtually dictator: only three copies of his book survived the fire. The Catholic Church also condemned him but, being a week or so too late, had to be content with burning him in effigy! Unfortunately, isolated quotations give a false idea of the precision of Serveto's views on the pulmonary circulation for he believed that the blood was in open communication with the trachea, and his concept of the rest of the movement of the blood was a mediæval fantasy. All his ideas were subservient to his theological doctrines and astrological beliefs and there is no evidence that he ever made any personal observations or experiments; it is possible that, as we shall see, he got his ideas from another source. There is, however, reason to believe that Vesalius saw some manuscript pages of Serveto's *Restitutio* (Robertson).

When Vesalius was Professor of Anatomy at Padua he had an assistant, Realdo Colombo, a man of comparatively little originality, who published nothing in his life-time, but wrote a text-book of anatomy which was published in 1559 after his death. This has been described as " an almost bare-faced imitation of Vesalius " (Foster) but it was certainly clearer, more concise, and didactically superior (Bayon). For this reason anatomists of Harvey's time preferred Colombo to Vesalius and his book contains one paragraph which must have been known to Harvey: " Between the ventricles is a septum through which almost all think there is a way from the right ventricle to the left. . . . This, however, is an error for the blood is carried by the arterial vein [pulmonary artery] to the lung. . . . It is brought back, together with air, by the venal artery [pulmonary vein] to the left ventricle of the heart. . . ." Although many believe that he got this idea from Serveto, whose book was published six years earlier, it is equally possible that the reverse is true, for Colombo was teaching anatomy in Pisa in 1545, and the earliest known manuscript of Serveto's book was dated 1546. Further, Colombo gave a clear and convincing anatomical account, together with the observations and experiments on which his views were based. Bayon has suggested that Colombo may have got the basic idea from another source for a translation of the 13th-century arabic writings of Ibn an-Nafis (1210–88) was published in Venice in 1547, twelve years before Colombo's book. Ibn an-Nafis knew of the pulmonary circulation for he described how the blood passes through the pulmonary artery " reaches the lungs, spreads in its substance, mixes with the air and flows in the venous artery [pulmonary vein] so as to be sent to the left of the heart ventricles." No one knows how Ibn an-Nafis got his information for he rejected both anatomical examination and experiments on animals. The importance of his writings has become known through the work of Meyerhof in 1935, but it does not seem likely that they influenced Colombo's views, for it is now known that the 1547 translation of his works did not contain the account of the pulmonary circulation.

It has been claimed that a pupil of Colombo, Andrea Cesalpino, anticipated Harvey's discovery of the circulation. It is probable that he adopted Colombo's views on the pulmonary circulation but, as Osler pointed out, Cesalpino believed that blood was distributed through the body by the veins for the nourishment of all its parts, and when a vein was ligatured " the blood behaved like a scared hen and rushed back in the contrary direction." By *circulatio* he seems to have meant efflux and reflux of the blood in the veins, in conformity with Galen's views. Though it may reasonably be claimed that the character of the pulmonary circulation had been recognized before Harvey's time, and the obstacle of the imperforate ventricular septum overcome, it is equally clear that the circulation from arteries to veins was unrecognized, and the obstacle to the flow of blood between them was regarded as absolute.

Robert Fludd was also a physician and a censor of the College on three occasions, although he

The principal known facts that might at that time have raised doubts were the valves of the heart and of the veins. It must have been difficult to see how the reflux of arterial blood took place through the aortic valve into the left ventricle, and the valves of the veins presented a similar problem. Harvey's attention was drawn to these by Giralomo Fabrizio, Professor of Anatomy in Padua when Harvey studied there. Fabrizio was a very learned man and must have influenced Harvey deeply for the two subjects that Harvey followed throughout his life—the circulation and embryology —were also the principal interests of Fabrizio. He was an able observer and an attractive teacher but in ideas he was gripped by the fetters of tradition, accepting fully the views of Aristotle and Galen. He certainly lectured on the valves of the veins in Harvey's time at Padua, for he first noticed them in 1574 and published his description in 1603. To us it seems obvious that they would prevent the flow of blood to the periphery. As, however, this was incompatible with the views of Galen, Fabrizio assumed that their function was merely to slow down the peripheral flow of blood, and he fully accepted Galen's view of the ebb and flow of venous blood. Robert Boyle (1627–91), well known as a pioneer in chemistry, wrote in 1688 that he had asked Harvey what things induced him to think of the circulation of the blood, and Harvey answered that he had taken notice of the valves in the veins, so placed that they gave free passage to the blood towards the heart, but opposed the contrary way, and " since the blood could not well, because of the interposing valves, be sent by the veins to the limbs, it should be sent through the arteries, and return through the veins, whose valves did not oppose its course that way."

The Discovery of the Circulation

So, in 1602, Harvey returned home to England probably familiar with almost all the observations and opinions so far discussed. In the same year he took his Cambridge M.D., in 1604 he was admitted by examination to the Royal College of Physicians, and in 1607 became a Fellow. Two years later he was appointed Assistant Physician at St. Bartholomew's Hospital and soon built up a practice which included many distinguished patients, notably Charles I and Francis Bacon. In 1615 he was appointed Lumleian Lecturer at the Royal College and almost certainly included his concept of the circulation in his first lectures in 1616. He must have developed his idea of the circulation between 1602 and 1616. Amongst the Englishmen of the time, who may have influenced his approach, three stand out: William Gilbert (1544–1603), Robert Fludd (1574–1637), and Francis Bacon (1561–1626).

Francis Bacon, who had advanced ideas and great gifts of exposition, made a profound impression in his own time and on subsequent generations; but he was more philosopher than scientist. He profoundly believed in experiment, but has been described as a " most enthusiastic but futile experimenter." He was modern in his belief in the advancement of knowledge, but clung to many mediæval ideas, some of which had already been refuted by the very methods he advocated. He devised a complete scheme for the experimental investigation of natural phenomena, which neither he nor anyone else ever used. He was a patient of Harvey's and of him Harvey said " He writes philosophy [science] like a Lord Chancellor; I have cured him of it." Although Francis Bacon did so much to propagate ideas about the advancement of knowledge, he did not himself contribute to knowledge in any field, and he seems to have had little or no regard for the work of men like Gilbert and Harvey who did, in fact, advance knowledge by Baconian methods. If we are to believe Harvey, the feeling was mutual.

William Gilbert was a physician of Colchester, but he is known for his work on magnetism. He was President of the Royal College of Physicians in 1600 and died in 1603, the year after Harvey returned to England. He was one of the first really successful experimentalists. He realized that the earth was a huge magnet and devised a primitive compass. Of him Dryden wrote (in somewhat dated lines):

" Gilbert shall live till lodestones cease to draw
Or British fleets the boundless oceans awe."

He was truly of Harvey's spirit and from him Harvey may have learnt the need to test hypothesis by experiment, and an essential criterion of a good experiment, namely that it can be repeated.

Robert Fludd was also a physician and a censor of the College on three occasions, although he himself had some difficulty in passing the College examinations. He was the first practising physician to try to explain pathological processes by experiments, though it has been said that " he drowned his results by much irrelevant speculation." Harvey certainly knew him, and if he gained anything from him, he was also a loser, for he sent *De Motu Cordis* to Fludd's printers in Germany and a shocking piece of work they made of it.

We can probably safely conclude that Harvey owed much less to his English contemporaries than to his experiences in Padua. It is, of course, impossible to be certain of the way in which Harvey built up the idea of the circulation if, indeed, he himself knew. From what he said to Boyle it is possible that the structure of the venous valves was his starting point. He was very certain of the course of the pulmonary circulation, though he wrongly attributed this observation to Galen. He wrote: " From Galen, that divine man, that Father of Physicians, it clearly appears that the blood passes through the lungs from the venal artery [pulmonary artery] to the small branches of the venal artery [pulmonary vein]." He had clear views on the function of the pulmonary and aortic valves—" once the blood has entered one of the great arteries it cannot return by the path it came. Its movement in that direction is absolutely stopped by valves."

But it is relatively unimportant how Harvey conceived of the motion of the blood " as it were in a circle." It is much more important to know that he set about testing his hypothesis and to see what methods he used to do so, for it is in this that his claim to greatness lies. Most of those who worked before him had been content with the plausibility of their ideas or sought confirmation only in authority, but Harvey recognized the need to test the truth of his, and by the techniques he chose, he played an important part in laying the foundations of the scientific method. In the first sentence of *De Motu Cordis* he wrote: " In discussing the movements and functions of the heart and arteries we should first consider what others have said on these matters, and what the common and traditional viewpoint is. Then by anatomical study, *repeated** experiment and careful observation we may confirm what is correctly stated, but what is false make right " (Leake translation).

Harvey used two methods of test. First, a quantitative mathematical approach in which he showed that the heart output in half an hour must greatly exceed the total amount of blood in the body. Since, Harvey wrote, the aortic valve prevents reflux into the ventricle, where could so much blood go to, or come from? It could only go to the veins, and thence return to the heart. How it got from the arteries to the veins, Harvey did not know, for the capillaries were not discovered until Malpighi demonstrated them in 1661. Although Harvey's calculations were sketchy and inadequately developed and considerably underestimated the output, they implied a way of thought that only Leonardo had previously used. Secondly, Harvey devised a series of testing experiments which showed the direction of blood flow in the veins, the efficiency of the venous valves, and attempted to show the passage of blood from the arteries to the veins.

A few men in every age from classical Greece and before had sought knowledge by experiment but not much had been gained because most experiments were ill-conceived and inconclusive or misleading. For instance, Galen attempted to demonstrate that the pulsation in an artery is transmitted by its wall and not by the contained blood. To do this he inserted a quill in the artery and found that the pulsation stopped beyond the quill. Bayon suggests that this was because he used a blocked quill and did only one experiment. Harvey made a significant contribution to the experimental method owing to his conviction that to be conclusive experiments must be repeated by the investigator and repeatable by others. Because his experiments were of this kind and because the hypothesis they were designed to test was well conceived, Harvey was able to show that the experimental method was capable of leading to significant advances in knowledge. Harvey's contribution was not so much the conception of experimental investigation, for there were others who had used it before him, but the success which he achieved by the way he used it. Consequently, the way in which Harvey's methods and conclusions came to be accepted is of importance in the development of the scientific method.

* My italics.

Reactions to "De Motu Cordis"

For twelve years, from 1616 to 1628, Harvey's Lumleian lectures in London almost certainly included a description of the circulation of the blood, but seem to have attracted no attention, although they were attended by many Fellows of the College. *De Motu Cordis* was published in 1628 in Frankfurt. It was a badly printed book of 72 pages of poor paper which perished in time, so that only 35 copies are now known to exist. After its publication the first printed comment came in 1630 from a Hull physician Primerose whom Harvey had examined as a Censor of the College. Primerose roundly denied the truth of Harvey's work in a book which he wrote in two weeks. The first approval came from Fludd, who may have been prejudiced for he was friendly with Harvey. In 1635 Emilio Paragiano (1567–1643) of Venice also condemned Harvey and wrote of the heart sounds, which Harvey mentioned: "Our poor deaf ears, nor any physician in Venice can hear them; thrice fortunate those in London who can." Descartes, the philosopher (1596–1650) accepted Harvey's views in 1636, though Bayon doubts whether he ever understood them. In 1639 a Venetian physician Folli (1615–50) also accepted Harvey's work but only because he believed that Galen had advanced the same idea. Glisson (1597–1677), when Regius Professor of Physic at Cambridge, is known to have been an early adherent of Harvey. But, in fact, between 1628 and 1640 little criticism or praise was published, and Harvey's work seemed more likely to perish from neglect than from criticism.

After 1640, however, support started to come from Ent in Cambridge and from Holland, where many distinguished physicians were convinced. A series of criticisms then appeared based mainly on the very different appearance of arterial and venous blood, for many found it difficult to believe that they were the same fluid. An interesting conversion was that of Plempius (1601–71) of Louvain who originally criticized Harvey, but later performed some experiments in dogs and subsequently acknowledged that Harvey was correct. This seems to represent a new spirit in science, and one not universally embraced even today! By 1648 prominent men in England, France, Germany, Holland, and even Padua had accepted Harvey's views. In 1651 Nathaniel Highmore wrote the first English anatomical work in which the circulation of the blood was fully recognized; it was appropriately dedicated to Harvey. Like Boston today, Italy, the cradle of so much that was growing in medicine, was hard to convince, but in 1651 the first open Italian support came from a physician of Rome, Giovanni Trullius, whose convincing experiments converted many sceptics. Harvey himself is quoted as saying that no man over forty admitted the truth of the circulation, but he was fortunate enough to live to see a widespread acceptance both of his conclusions and his methods, and the fact that his experiments could be repeated by men like Plempius in Belgium and Trullius in Rome undoubtedly contributed to this happy outcome.

Harvey was not a rebel or a firebrand, but a careful, persistent, and unprejudiced investigator, with an almost exaggerated respect for the views of his predecessors. The methods available in his time for testing physiological hypotheses were few and limited in scope, but such as they were he used them persistently and patiently throughout his life, not only in *De Motu Cordis* but also in his later work *De Generatione*. He well represents the age that learnt to loosen the bonds of dogma by experiment and observation. The 17th century has been labelled the century of genius, for it produced such scientists as Boyle and Isaac Newton, such philosophers as Descartes and Spinoza, and men of vision like Francis Bacon, Hobbes, and Liebnitz. It laid the foundations of science, of political freedom and democratic government, of religious toleration, and of freedom of speech. It is not surprising that Whitehead wrote in *Science in the Modern World*: "A brief and sufficiently accurate description of the intellectual life of the European races during the succeeding two centuries and a quarter up to our own times is that they have been living upon the accumulated capital of ideas provided for them by the genius of the seventeenth century." It is true that there is still no sign of any new development of thought comparable with the radical change of outlook that was beginning to gather force three centuries ago. Although there is no reason to suppose that the potentialities of the scientific method are becoming exhausted, it is obvious that it has limitations which are particularly pertinent in our times when science seems almost as likely

to destroy our civilization as to enhance it. With Pope we must sometimes be troubled by the contrast between man's increasing power over his environment and his inadequate control over himself

> " Go, wondrous creature! mount where Science guides
> Go, measure earth, weigh air and state the tides,
> Instruct the planets in what orbs to run,
> Correct old Time, and regulate the sun;
> Go teach Eternal Wisdom how to rule—
> Then drop into thyself, and be a fool."

In the words of Bertrand Russell (*The Scientific Outlook*) " Not all wisdom is new, nor is all folly out of date." Perhaps that is not an inappropriate motto for these lectures.

My debt to Bayon's scholarly articles on Harvey and his contemporaries will be obvious to all familiar with his work (*Ann. Sci.* (1938) **3**, 59, 435, and (1939) **4**, 65, 329; *Proc. Roy. Soc. Med.* (1938), **32**, 31; and (1951) **44**, 213). An excellent selected bibliography of writings on Harvey has been published by the Wellcome Historical Medical Library (*Current Work in the History of Medicine*, 1956, **9**, 57) and I am indebted to the librarian, Dr. F. N. L. Poynter, for much advice and information. I have used the Leake Translation of *De Motu Cordis* but I have found it helpful to compare this with the original whenever possible. In a general review of this kind it is neither desirable nor possible to enumerate all the sources consulted but some of the more important are mentioned in the text.

PULMONARY HYPERTENSION IN MITRAL STENOSIS

BY

WILLIAM EVANS AND D. S. SHORT

From the Cardiac Department of the London Hospital

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It is known that the pulmonary arterial pressure is raised in many patients with mitral stenosis, and that in a proportion of them the abnormal resistance to the blood flow in the pulmonary arterial bed gives rise to persistent pulmonary hypertension. Although this state, which may influence prognosis and prove important in the selection of patients for surgical treatment, has received some attention, it has not yet been adequately investigated.

In a previous paper (Evans *et al.*, 1957) we described the pulmonary vessels in 11 patients with solitary pulmonary hypertension. Our present paper is concerned with the state of these vessels in patients with mitral stenosis, with the significance of the changes, and with their recognition during life.

The presence of naked-eye changes in the pulmonary arteries in mitral stenosis has long been recognized. Thus, Posselt (1909), reviewing all the cases of pulmonary arteriosclerosis published during the nineteenth century, found that mitral stenosis was responsible for 40 per cent of them. It was Parker and Weiss (1936) who first described the microscopical changes; they examined 23 cases and found severe pulmonary arterial lesions in five of them; these included atheroma complicated by thrombosis in the larger arteries, intimal thickening in the muscular arteries, and concentric cellular proliferation in the arterioles. Larrabee *et al.* (1949) reported arterial lesions in 18 out of 20 cases of well-established mitral stenosis, and remarked that they were most prominent in vessels of 0·15 to 0·05 mm. diameter. In neither of these investigations were the histological changes related to the presence or absence of pulmonary hypertension. Henry (1952) described the presence of an abnormal muscular coat in the arterioles in 40 per cent of 105 cases of mitral stenosis, but he found it in none of 70 control cases. This abnormality has also been reported by Soulié *et al.* (1953) and Heath and Whitaker (1955) have emphasized its association with pulmonary hypertension.

Almost all workers are agreed that the walls of many of the muscular arteries in mitral stenosis appear abnormally thick and have described the change as medial hypertrophy. O'Neal *et al.* (1955) undertook a special study of the media of the small muscular pulmonary arteries in 67 cases of moderate or severe mitral stenosis whose average age was 55 years, and compared the findings with those in a control series of comparable age without heart disease. They selected for measurement muscular arteries that were situated near a bronchiole and in order to avoid the discrepancy introduced by variation in the degree of arterial contraction, they calculated the area of the media at each cross-section of the vessel. By this method they failed to demonstrate any significant difference in the amount of arterial media in the two series, and they concluded that although the arteries were smaller there was no medial hypertrophy. They were also unable to identify a medial coat in the arterioles.

The relationship between the vascular changes and the presence of pulmonary hypertension has not yet been resolved. Several workers have tried to correlate arterial changes found on lung

biopsy or at necropsy with observations made during cardiac catheterization. The amount of lung available for scrutiny is small, however, and single records of the pulmonary arterial pressure are unreliable. Moreover, the diagnosis of pulmonary hypertension should not rest on such evidence, but on clinical, electrocardiographic, and radiological examination.

Apart from the nature of the vascular changes there is the further problem of their extent. This cannot be determined by the examination of discrete histological sections, for these do not provide adequate information on the state of the arterial bed as a whole. Goodwin *et al.* (1952) recorded pulmonary arteriograms in patients with mitral stenosis, and demonstrated abrupt narrowing of the peripheral arteries in those with severe pulmonary hypertension. Although such an investigation is informative, the authors were aware that it could not distinguish between structural arterial narrowing and arterial spasm whether due to mitral stenosis or provoked by the contrast medium. Pulmonary arteriography at necropsy (Evans, 1951; Short, 1956) is the best means of demonstrating the site, the severity, and the extent, of organic disease affecting the pulmonary vasculature.

The Investigation Described

A routine clinical, electrocardiographic, and radiological examination of the chest, was made in 24 patients in whom mitral stenosis was confirmed at necropsy, special attention being paid to the diagnosis of pulmonary hypertension. Thirteen were women and eleven men. The ages varied from 16 to 69, and the average age was 44 years.

At necropsy, the heart was weighed, and the degree of right ventricular hypertrophy was

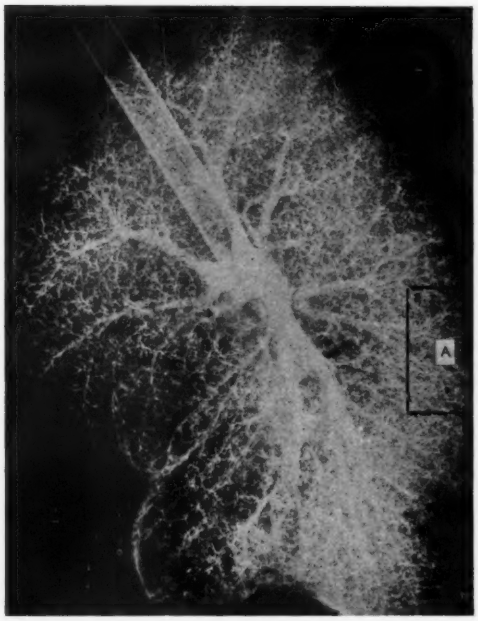

Fig. 1.—Pulmonary arteriogram from a patient with mitral stenosis without pulmonary hypertension. Apart from two filling defects from thrombotic occlusion the peripheral vessels are normal. Segment (A) has been magnified in Fig. 3A.

Fig. 2.—Pulmonary arteriogram from a patient with mitral stenosis and pulmonary hypertension. The basal artery and several smaller ones are obstructed by thrombus, but the generalized loss of the finest branches has much greater significance. Segment (B) has been magnified in Fig. 3B.

estimated by measuring the thickness of its wall and comparing it with that of the left ventricle. The size of the mitral valve orifice was also determined.

The lungs were examined according to the procedure described in our paper on solitary hypertension (Evans *et al.*, 1957). A pulmonary arteriogram was performed in 12 of the cases. A detailed histological examination was made in all, an average of five blocks of lung tissue being taken including sections from an upper and a lower lobe.

The Pulmonary Vascular Changes

Naked-eye examination of the pulmonary arterial trunk and its main branches revealed dilatation, atheroma, and thrombosis or embolism, but the changes specifically related to pulmonary hypertension came to light only when the finest arteries were examined by a combination of pulmonary arteriography and histology.

The Pulmonary Arteriogram

The arteriogram was abnormal in each of the 12 cases in which it was carried out. The changes were of two kinds, focal and diffuse. The *focal changes*, present in every case, included thrombotic obstruction of segmental arteries, especially those to the lower lobes, areas of infarction, and abnormal anastomoses between branches of the pulmonary artery and between bronchial and pulmonary arteries. The *diffuse changes*, present in 6 of the 12 cases, consisted of an absence of

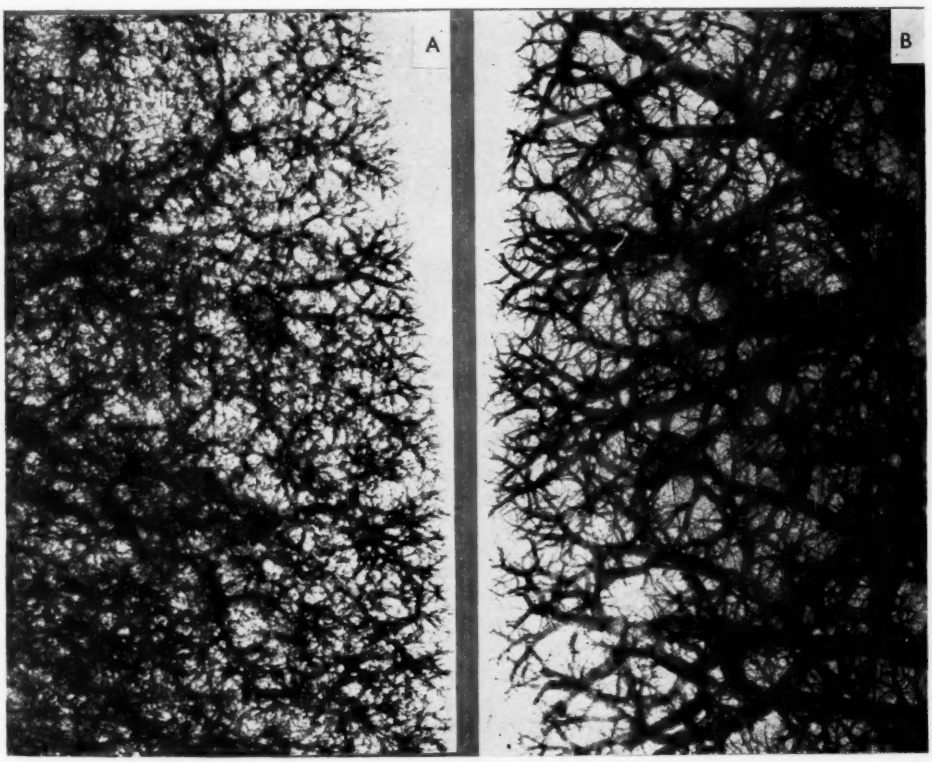

FIG. 3.—Magnified pulmonary arteriogram; (A) is from arteriogram shown in Fig. 1, and (B) from Fig. 2.

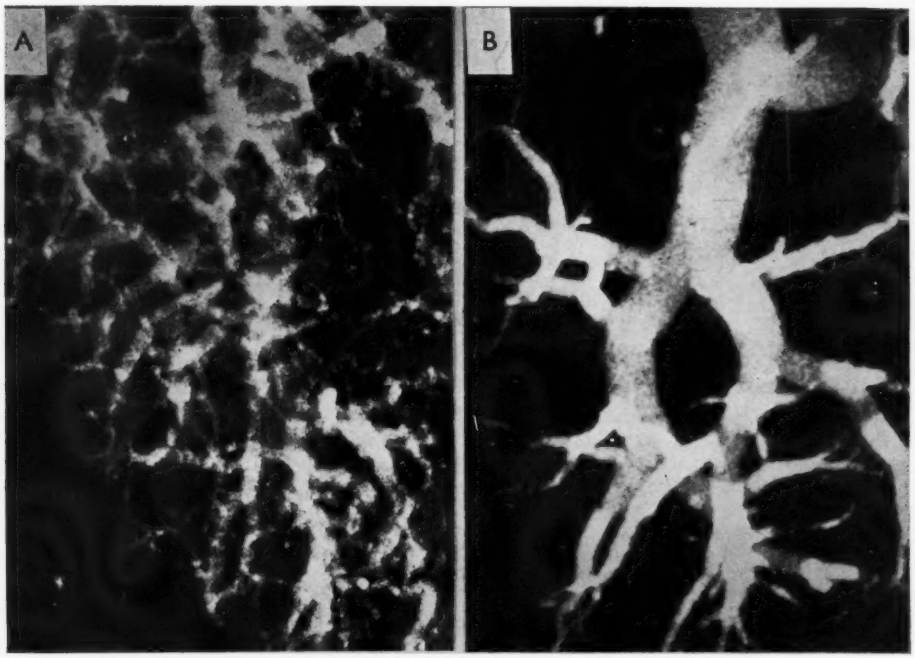

FIG. 4.—Magnified pulmonary arteriograms. (A) is from a patient with mitral stenosis without pulmonary hypertension. (B) is from a patient with mitral stenosis and pulmonary hypertension.

opaque material from the finest branches throughout the lungs. This denuded appearance could be seen in arteriograms of the whole lung (Fig. 2), but was more noticeable in magnified films (Fig. 3A and B and 4A and B), or in contact prints of lung sections, 1·0 cm. thick (Fig. 5); it was even obvious on inspection of the cut surface (Fig. 6). The lost branches were mostly of arteriolar size. Arteries greater than 0·1 mm. diameter were also sometimes occluded, and even when patent they were frequently smaller in calibre than the corresponding arteries from normal lungs or from cases of mitral stenosis showing only focal changes. The segmental arteries to the lower half of the lung were also constricted; the bore of these narrowed arteries was sometimes smooth, but in other instances atheromatous plaques caused indents in the stream of injected material.

The Histological Changes

The vascular changes found on histological examination corresponded with those observed in the arteriogram, and were likewise of two kinds, namely subsidiary and salient.

The *subsidiary changes* were common to all 24 cases. Thus, there was intimal thickening in the elastic arteries in excess of that met with in subjects of a comparable age with normal lungs. There was thrombosis of one or more segmental arteries and even of the pulmonary arterial trunk in two cases. The bronchial arteries in their extra-pulmonary course were normal, but the opaque medium invariably flowed from these vessels during injection of the pulmonary artery, indicating the presence of abnormal broncho-pulmonary arterial anastomoses; there was often a plethora of bronchial arteries within the lung. The capillaries were frequently compressed by thickening of the alveolar septa. The venules were narrowed by the presence beneath the intima of an acellular eosinophilic material (Fig. 7). Thrombosis in the large pulmonary veins was met with in a few instances.

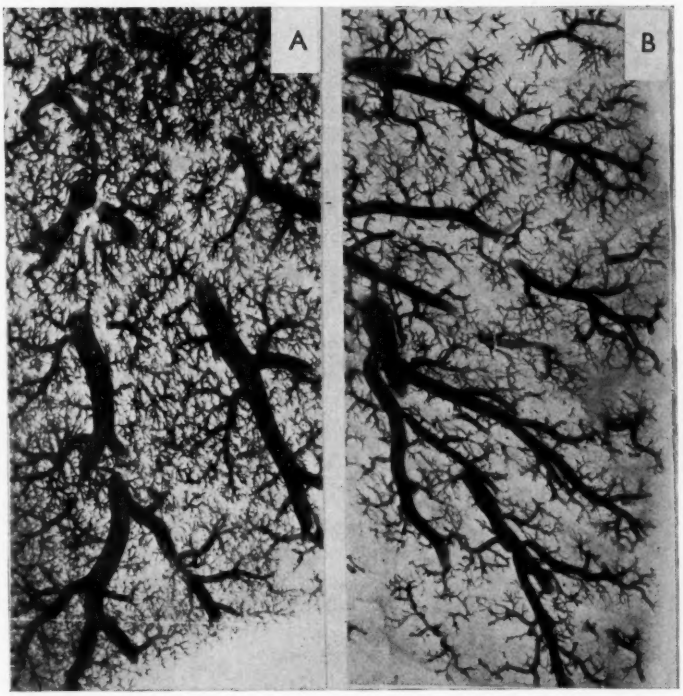

FIG. 5.—Arteriogram of section of lung 1 cm. thick. (A) is from a patient with uncomplicated mitral stenosis. (B) is from a patient with mitral stenosis and pulmonary hypertension.

The *salient changes*, found in 12 of the 24 patients, were of two kinds. The one was great and widespread intimal proliferation and the other was refractory arterial contraction. The combination of the two processes had led to both narrowing and occlusion of arterioles and small muscular arteries throughout the lung. Whenever an arteriogram had been carried out, it always demonstrated the diffuse changes indicating obstruction of the smaller vessels.

The finding of a few contracted arteries, or the presence of slight and localized intimal proliferation, did not qualify a case for inclusion among those with salient changes, for contracted arteries were found in two cases without important intimal proliferation, and it is known that slight intimal thickening may be found in otherwise normal lungs (McKeown, 1952). Localized intimal proliferation usually gave the impression that it had been thrombotic in its inception.

The presence in vessels of arteriolar size of a distinct muscular coat lying between two elastic layers was a feature of all the twelve cases with salient changes. This change was frequently present in vessels of 0·07 mm. diameter, and occasionally in ones as small as 0·04 mm. (Fig. 8). We regard these, not as " muscularized " arterioles, but as muscular arteries in an abnormal state of contraction. In each of these cases the media of the slightly larger muscular arteries appeared unusually thick, and although this has generally been interpreted as evidence of hypertrophy, we regard it as evidence of refractory arterial contraction.

Intimal proliferation was always severe in the arterioles and gave rise to a characteristic appearance. Thus, layers of endothelial cells with their elongated nuclei were arranged concentrically in

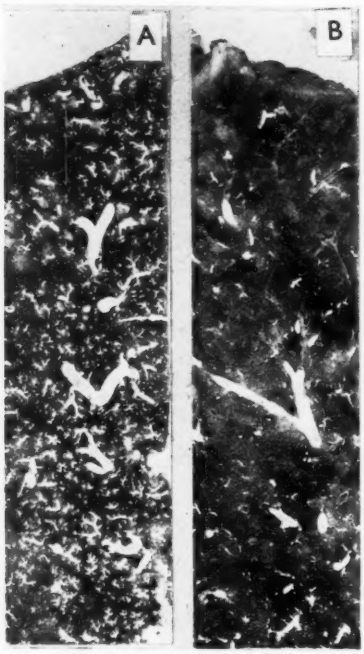

FIG. 6.—Cut-section of injected lung. (A) is from a patient with uncomplicated mitral stenosis. (B) is from a patient with mitral stenosis and pulmonary hypertension.

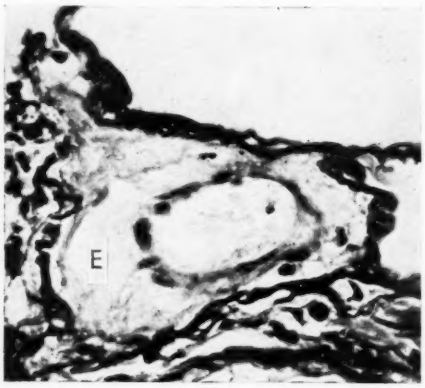

FIG. 7.—Venule (×500) from a patient with mitral stenosis, showing subintimal deposition of acellular eosinophilic material (E).

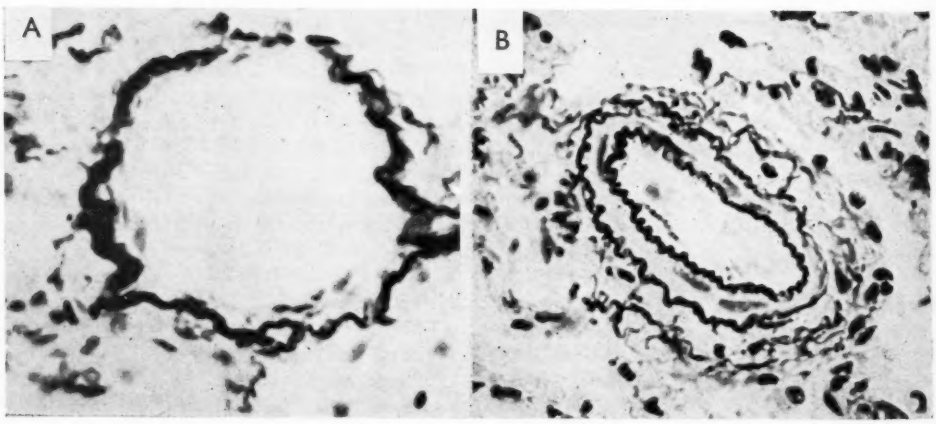

FIG. 8.—Contracted small muscular pulmonary artery (B) (×500) from a patient with mitral stenosis and pulmonary hypertension, compared with a normal arteriole (A) (×500) from a patient with uncomplicated mitral stenosis.

a whorl-fashion and the nuclei of the innermost layer were often disposed radially giving rise to a pallisading effect (Fig. 9). In one case there was widespread arteriolar necrosis.

In four of the twelve there was extensive intimal proliferation in the small muscular arteries as well as in the arterioles, and in these vessels the intimal thickening was associated with hypoplasia of the media (Fig. 10). This deficiency usually affected only a segment of the vessel wall, but occasionally the entire media was lost giving the impression of an arteriole. Such deficiencies were also present, though less frequently, in the eight cases where the intimal proliferation affected the arterioles more than the small muscular arteries.

Changes in the Heart

The heart was always heavier than normal. In those with salient pulmonary vascular changes the weight varied between 340 g. and 675 g. with a mean of 470 g., compared with 300 g. as the upper limit of normal. In those with only subsidiary vascular changes, the weight varied between 350 g. and 980 g. with a mean of 620 g. The heaviest hearts were those from patients with associated aortic valve disease.

Hypertrophy of the right ventricle was significantly greater in cases with salient pulmonary vascular changes than in those showing only subsidiary changes. Thus, in the first group, the maximum thickness of the free wall of the ventricle ranged from 6 to 13 mm. with a mean of 9 mm., while in the second group it ranged from 3 to 8 mm. with a mean of 5 mm. In cases with right ventricular hypertrophy, there was usually dilatation and hypertrophy of the right auricle as well. Intracardiac thrombosis was present in six of the cases with salient pulmonary vascular changes, involving the left auricle in five (mass thrombus in two), the right auricle in one and the left ventricle in one. In the group with subsidiary changes, thrombosis was present in eight cases, involving the left auricle in eight (mass thrombus in one), the right auricle in one, and the left ventricle in one.

There was no correlation between the incidence of salient pulmonary arterial disease and the size of the mitral orifice. A reasonably accurate estimate of the size of the opening could be made in 20 of the 24 cases. In 10 of these, with salient vascular changes, the stenosis was severe (15 mm. or less in length) in 9: in the tenth the mitral orifice was 25 mm. long and 8 mm. wide with heavy calcification of the valve; although there must have been obstruction to the blood flow in this case, the presence of considerable left ventricular hypertrophy indicated substantial mitral incompetence. In the 10 patients with subsidiary vascular changes, the stenosis was severe in 7 and moderately severe (18 to 25 mm. in length) in 3: the most severe stenosis (6 mm. by 4 mm.) in the entire series was found in one of these cases in whom the right ventricle was only 4 mm. thick.

The Diagnosis of Pulmonary Hypertension when Associated with Mitral Stenosis

Having established by pulmonary arteriography and histological examination, the relationship between specific changes in the lesser pulmonary arteries and the occurrence of pulmonary hypertension in mitral stenosis, we now compare the clinical features in the 12 cases showing salient pulmonary arterial changes and pulmonary hypertension, with those presented by the 12 cases showing only subsidiary pulmonary arterial changes without pulmonary hypertension.

Age. The patients with pulmonary hypertension became disabled at a younger age than those without. Thus, the age at death ranged from 16 to 48 with a mean of 35 years in the first group, compared with 38 to 69 with a mean of 52 years in the second group, even though aortic valve disease also was present in 7 of them.

Sex. Of the 12 patients with pulmonary hypertension, nine were women, compared with four women among the 12 without pulmonary hypertension.

Physical Signs. The presence of pulmonary hypertension in mitral stenosis supplies its own characteristic signs which include a small pulse, raised venous pressure, a prominent auricular wave in the neck if sinus rhythm is present, predominant right ventricular pulsation, a loud pulmonary second sound, a sound in early systole, and occasionally a Graham Steell murmur.

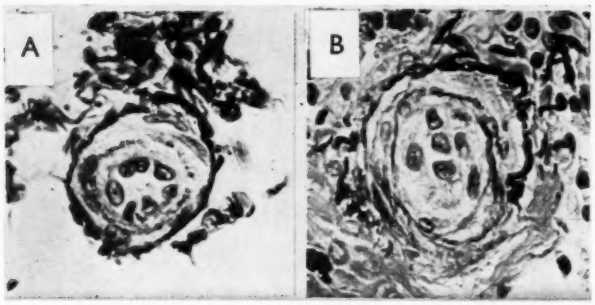

FIG. 9.—Arterioles (×500), partly closed in (A) and wholly closed in (B) by intimal proliferation, from two patients with mitral stenosis and pulmonary hypertension. The pallisading appearance in (A) is characteristic.

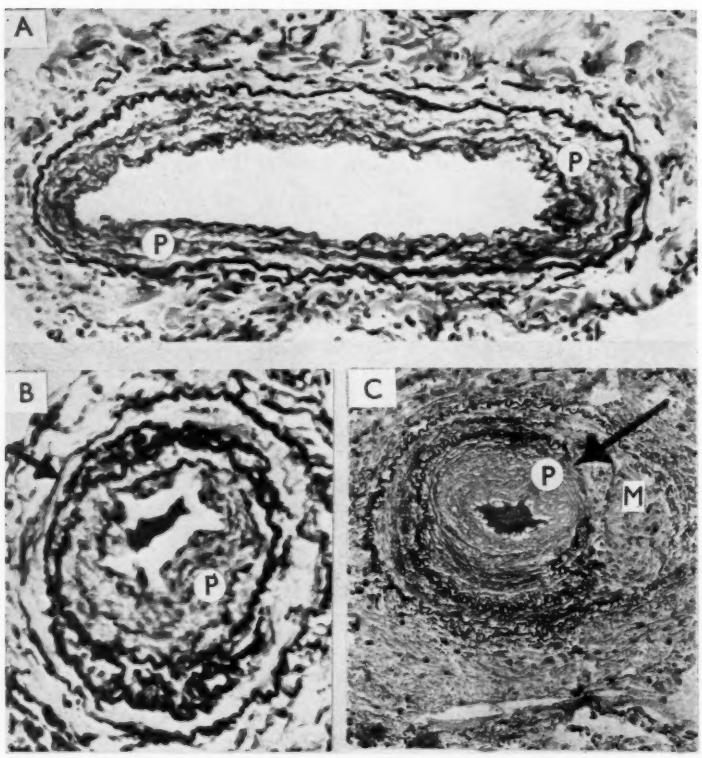

FIG. 10.—Small muscular pulmonary arteries in three patients with mitral stenosis and pulmonary hypertension, showing intimal proliferation (P). In (A) (×200) there is general medial hypoplasia especially at the base of the picture. In (B) (×300) the site of the medial hypoplasia is indicated by the arrow (top left-hand corner). In (C) (×100) a break in the internal elastic layer is indicated by the arrow; the intimal reaction here may be thrombotic in origin. Adjacent to this is an area of medial necrosis (M).

The Electrocardiogram. The electrocardiogram showed right ventricular preponderance (Fig. 11 and 12) in each of the 12 patients in whom salient pulmonary arterial changes were found on arteriographic and histological examination. Thus, in CR_1 or V_1 the R wave was greater than the S in every case; the S was only slightly smaller than R in three, diminutive in four, and absent in five. Whenever V_4R was recorded it confirmed the right ventricular preponderance. An S wave was always present in lead I; it equalled the R wave in three, and exceeded it in nine cases. An S wave was present in CR_7 in all save three patients, and the R wave was never tall in this lead. S-T depression was always obvious in lead III, and also in a lesser degree in lead II, though in many patients this deformity was exaggerated by digitalis therapy. The T wave in CR_1 or V_1 was inverted in the seven patients with normal rhythm; in the remaining five its direction could not be told because of the fibrillation waves.

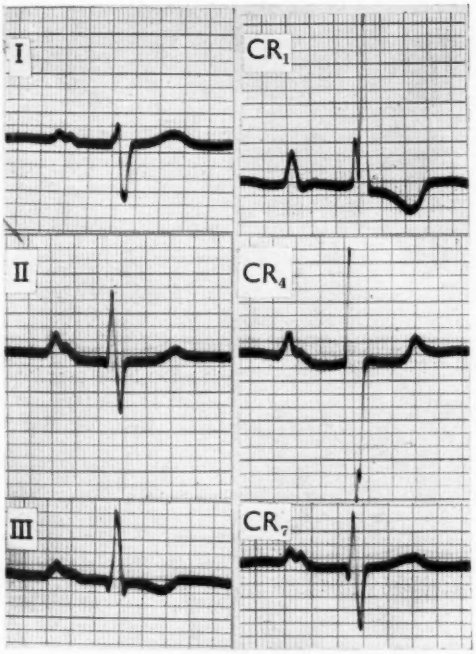

FIG. 11.—Right ventricular, and right and left auricular, preponderance in a patient with mitral stenosis and pulmonary hypertension. Both here and in Fig. 12 the horizontal lines indicate a voltage of 2 mm.

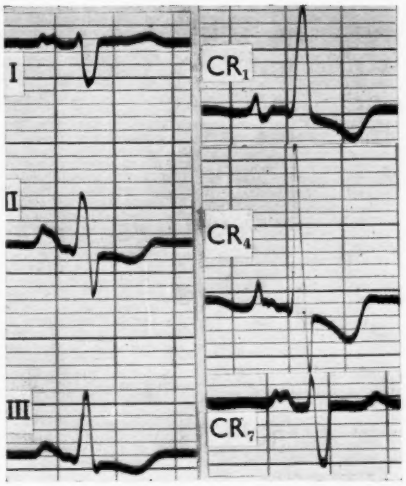

FIG. 12.—Right ventricular, and right and left auricular, preponderance in a patient with mitral stenosis and pulmonary hypertension.

In the patients with mitral stenosis who showed only subsidiary changes in the pulmonary arteries these signs of right heart preponderance were absent. An S wave was never found in CR_7 in this group and was present in lead I in only one half of them. In one the R wave did just exceed the S in CR_1, but there was no S in either lead I or CR_7.

A P wave that is 2·5 mm. high in CR_1 and at the same time diphasic, pointed, or bifid with a dominant first peak indicates right auricular preponderance and supports the diagnosis of pulmonary hypertension in mitral stenosis. Among our seven patients with mitral stenosis and pulmonary hypertension, who had remained in sinus rhythm, electrocardiographic evidence of right auricular preponderance was present in four.

This correlation between the histological and electrocardiographic changes emphasizes the importance of the electrocardiogram in the diagnosis of pulmonary hypertension in mitral stenosis.

Radiology. In the patients in whom mitral stenosis was associated with pulmonary hypertension, the heart usually appeared somewhat smaller than in those without hypertension, the majority of whom had aortic valve disease as well. Thus, in the first group the width of the heart in proportion to that of the chest ranged from 48 to 77 per cent with a mean of 60 per cent, compared with 54 to 74 per cent with a mean of 67 per cent in the second group.

A distinctive feature of the 12 cases with pulmonary hypertension was the prominence of the pulmonary trunk and its two branches. Although the pulmonary bay was partly or completely filled in the 12 cases without pulmonary hypertension (Fig. 13), in those with hypertension there was usually an actual bulge in the region of the pulmonary artery and the origin of its left branch. The segmental branches were narrow in four patients, probably narrow in one, natural in four, and obscured in the remaining three. In three patients the lung parenchyma appeared abnormally clear as in solitary pulmonary hypertension (Fig. 14), but in six there was conspicuous hilar and pulmonary clouding with distinct interlobular lines, changes characteristic of the indurated lung of mitral stenosis (Short, 1955) (Fig. 15). There was intense hæmosiderosis in one case (Fig. 16).

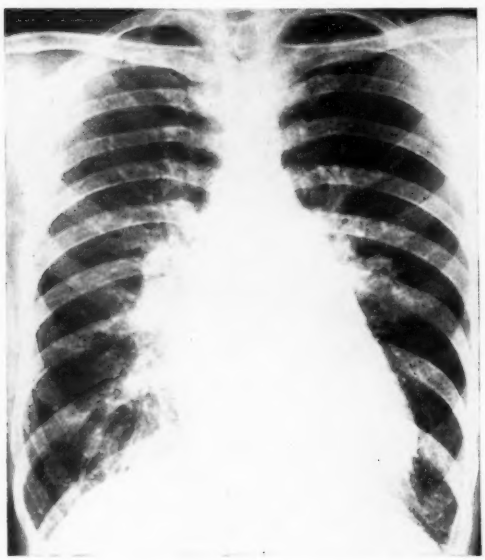

FIG. 13.—Uncomplicated mitral stenosis.

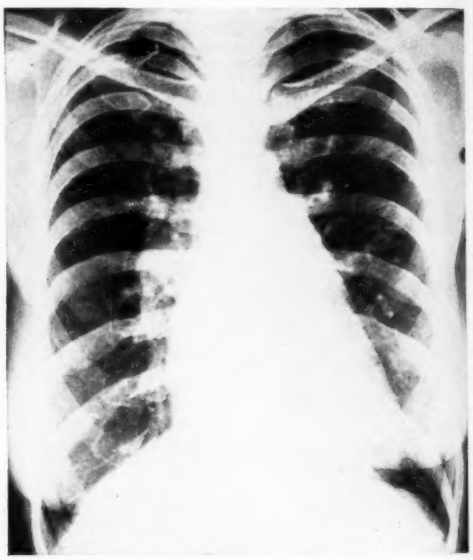

FIG. 14.—Mitral stenosis and pulmonary hypertension. It differs from Fig. 13 only in showing clearer lungs in the periphery.

Cardiac Catheterization. In all cases of significant mitral stenosis the pulmonary arterial pressure, and especially the pulmonary capillary venous pressure, is raised; the pulmonary vascular resistance is slightly increased, and the cardiac output diminished. When pulmonary hypertension is added, the pulmonary arterial pressure and the pulmonary vascular resistance are disproportionately raised, while the cardiac output is further reduced.

THE DIAGNOSIS OF MITRAL STENOSIS WHEN ASSOCIATED WITH PULMONARY HYPERTENSION

It is sometimes very difficult to recognize mitral stenosis when combined with pulmonary hypertension because the characteristic physical signs of the valvular lesion may be suppressed. A

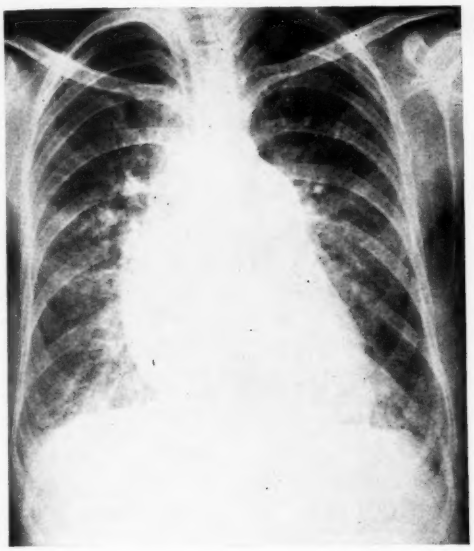

FIG. 15.—Mitral stenosis and pulmonary hypertension, showing great dilatation of the pulmonary trunk, right auricle and superior vena cava, and pulmonary clouding.

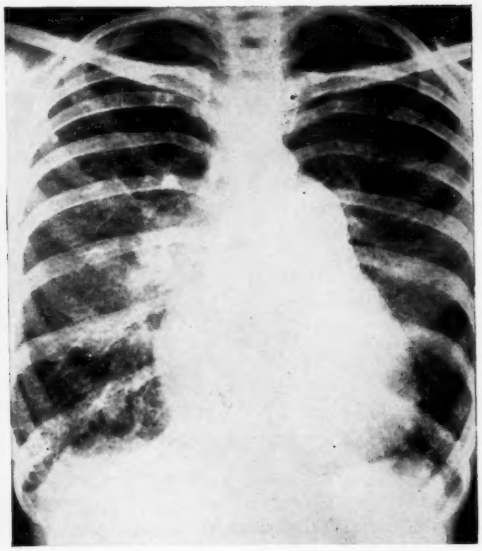

FIG. 16.—Mitral stenosis and pulmonary hypertension, showing great enlargement of the pulmonary trunk and right heart, with pulmonary clouding, interlobular lines and hæmosiderosis.

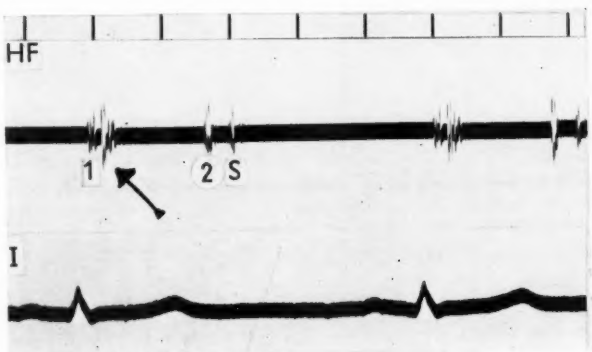

FIG. 17.—Mitral stenosis and pulmonary hypertension. Sound in early systole (arrow). Snap sound (S) in early diastole. No murmurs are present.

history of rheumatic fever in early life should be sought. If this is forthcoming and particularly if the patient was told at that time that his heart was affected, the presence of mitral stenosis becomes more likely. In other varieties of pulmonary hypertension sinus rhythm is usually preserved, so that if auricular fibrillation is present, as in five of our twelve cases, the association of mitral stenosis with pulmonary hypertension is a strong presumption. The diastolic murmur may disappear (Fig. 17), but the opening snap usually remains and so proves helpful in diagnosis, although rarely a snap sound in early diastole is found in solitary pulmonary hypertension (Evans *et al.*, 1957). When the presystolic and diastolic murmurs are inconstant or absent in suspected mitral stenosis associated with pulmonary hypertension, the diagnosis of myxoma of the left auricle has to be considered.

The electrocardiogram may assist the recognition of mitral stenosis when it occurs in association with pulmonary hypertension by demonstrating either auricular fibrillation or left auricular preponderance. A bifid P wave, 3·0 mm. high in CR_4 or CR_7 with a dominant second peak, or a peak interval of 0·04 sec. in any lead regardless of voltage (Thomas and de Jong, 1954), indicates left auricular preponderance, and this sign was present in three of our seven patients who remained in sinus rhythm (see Fig. 11 and 12).

The recognition of associated mitral stenosis is also helped by radiological examination of the patient in the oblique positions during a barium swallow, for enlargement of the left auricle confirms the presence of the valvular lesion. Such enlargement, however, is not always noticeable in mitral stenosis, so that a normal left auricular impression in the œsophogram does not exclude the diagnosis.

The Influence of Pulmonary Hypertension on Mitral Stenosis

Besides modifying the clinical, electrocardiographic, and radiographic signs identified with uncomplicated mitral stenosis, the addition of pulmonary hypertension may influence the course of the illness. A decision on this is needed preparatory to the selection of patients with mitral stenosis who are likely to gain the greatest benefit from surgical treatment, for at present the incidence of pulmonary hypertension is high among those selected for this form of treatment. Thus, 42 out of the first hundred cases so treated at the London Hospital had pulmonary hypertension.

We have gained the impression from reports hitherto published that many share the belief that the pulmonary vascular changes responsible for pulmonary hypertension in mitral stenosis are wholly reversible, and that this favourable outcome can be attained by surgical treatment of the stenotic mitral valve. Thus, Wood (1954) has said that no case of irreversible pulmonary hypertension had yet been encountered. Turner and Fraser (1956) have stated that evidence of right ventricular hypertrophy in the electrocardiogram, associated with signs of otherwise uncomplicated mitral stenosis, is a strong indication for operation. Mackinnon *et al.* (1956), although admitting that structural changes are probably concerned in the maintenance of pulmonary hypertension, nonetheless believe that the condition is reversible. Indeed, they have insisted that the presence of high vascular resistance should be recognized as an urgent indication for surgical treatment.

The combined arteriographic and histological examination of the pulmonary vasculature in our patients leads to the inescapable conclusion that the gross obstruction within the arterial system that is present in pulmonary hypertension must inevitably affect the prognosis adversely. Such intimal proliferation as we found seemed a progressive rather than a reversible process. In order to test this conclusion it is necessary to compare the post-operative course of patients with and without associated pulmonary hypertension.

There is no doubt that very high pressures may fall to near normal levels. Janton *et al.* (1956) followed 50 patients four and a half to seven years after valvotomy and found that in those with the highest pulmonary arterial pressures before operation the fall in pressure though gradual was ultimately profound. Thus in one patient, a pressure of 143/56 mm. Hg fell to 36/15; in another a pressure of 130/59 fell to 24/8, while in a third a pressure of 105/25 fell to 23/4 mm. Hg. Soulié *et al.* (1956) studied the hæmodynamic changes following valvotomy in 70 cases of severe uncom-

plicated mitral stenosis and their findings were similar to those of Janton *et al.* (1956). Soulié, however, excluded cases regarded as having chronic cor pulmonale secondary to mitral stenosis, having previously emphasized (Soulié *et al.*, 1953) the danger of general anæsthesia in this class of patient.

Baker *et al.* (1955) followed 45 patients with mitral stenosis for at least three years after valvotomy and concluded that those with severe pulmonary hypertension did well and maintained their improvement. Nevertheless, three of their six patients with mean pulmonary artery pressures exceeding 80 mm. Hg died following the operation, while among the 39 patients without extreme pulmonary hypertension there were only two immediate deaths.

Mackinnon *et al.* (1956) reported six cases of mitral stenosis with very high pulmonary vascular resistance and claimed that the pulmonary hypertension was reversible. The results which they publish do not, however, justify this view. Thus, one died of heart failure during medical treatment before the operation could take place. Of the five in whom valvotomy was carried out, one died 12 hours later in spite of good splitting of the valve; another was not improved and the right ventricular pressure had remained at 140 mm. of Hg; in another the pulmonary arterial pressure remained high (66/24 mm. Hg) although the capillary venous pressure had fallen to normal; the fourth case had not been recatheterized and continued to show some incapacity; and in only one was the result excellent.

Ferrer *et al.* (1955) studied the circulatory effects of mitral valvotomy in 27 patients. Of the 18 with severe pulmonary hypertension, the result was classed as excellent in only seven. Four died during or immediately following the operation, and two were not improved. Donald *et al.* (1956) recatheterized 28 patients 17 to 51 months after satisfactory valvotomy and found that, although the resting pulmonary artery pressures were reduced in all patients, very few approached normal values.

These reports show that in severe pulmonary hypertension mitral valvotomy may be followed by a considerable reduction in the pulmonary arterial pressure and the vascular resistance, and the fact that this reduction is gradual suggests that certain of the structural changes in the lung are reversible. Frequently, however, the pulmonary vascular resistance changes little in spite of a satisfactory fall in pulmonary capillary pressure and the progression of the disease may be unaffected by the operation.

Disappearance of electrocardiographic evidence of right ventricular hypertrophy following mitral valvotomy has been occasionally reported. In the series of 250 patients reported by Turner and Fraser (1956) 158 were judged to have right ventricular hypertrophy. Following the operation the signs of right ventricular hypertrophy had disappeared in 16 per cent, and had regressed variably in another 24 per cent. Among the 42 patients with mitral stenosis and pulmonary hypertension who underwent mitral valvotomy at the London Hospital, Mounsey (1956) reported that in no instance had the signs of right ventricular preponderance disappeared from the electrocardiogram after what appeared to have been an effective splitting of the stenosed valve. There is conclusive evidence, with which our experience agrees, that in patients with pulmonary hypertension and a greatly reduced cardiac output, the operation itself is a more hazardous undertaking. In such cases the greatest care must be taken in management by physician, anæsthetist, and surgeon, at the time of the operation and during the post-operative period.

The Cause of Pulmonary Hypertension in Mitral Stenosis

An increase in the pulmonary arterial pressure is inevitable if the circulation is to be maintained in the face of obstruction at the mitral orifice. What is considered here, however, is not this natural rise of pressure, but the more severe and sustained rise that develops in a proportion of patients. Dexter *et al.* (1950) showed that the immediate cause of this disproportionate pulmonary hypertension was an increased pulmonary vascular resistance, that formed a second barrier to the circulation in the pulmonary vessels in addition to the primary barrier at the mitral valve.

It might be assumed that this increased resistance would be related to the duration and severity of the mitral stenosis. Wood (1954), however, has shown that patients with pulmonary hypertension are on the average no older than those without, many being in the third and a few in the second decade. In regard to the severity of the stenosis, Becker *et al.* (1951) found the same high pulmonary vascular resistance in two patients whose dominant lesion was mitral incompetence. Our series has provided a similar example. Again, pulmonary hypertension is not closely related to the level of the pulmonary venous pressure, for Dexter *et al.* (1950) found that some patients with pulmonary capillary venous pressure in the twenties had much higher vascular resistance than others with a pressure (in mm. of Hg) in the thirties.

Opinion on the nature of the abnormal pulmonary vascular resistance in mitral stenosis is divided. It is probably true to say that the majority of workers in this field believe that it arises from pulmonary vasoconstriction. The main evidence put forward in support of this view is that the resistance may sometimes be reduced by the administration of such drugs as hexamethonium (Davies *et al.*, 1954; Wade *et al.*, 1956) and acetylcholine (Harris, 1955; Wood, 1956), and by valvotomy (Wood, 1954; Mackinnon *et al.*, 1956). It is not known with certainty whether the degree of vasoconstriction in patients with pulmonary hypertension is in excess of the physiological vascular tone, and if so what causes it. Wood (1956) maintains his earlier suggestion (Wood, 1952) that in certain subjects vasoconstriction develops in response to pulmonary hypertension itself.

Soulié *et al.* (1953) found a close parallel between the extent of the lesions in the alveolar septa and the degree of vascular resistance, and suggested that pulmonary hypertension was the result of this reduction in the pulmonary bed. In our series, however, the severity of parenchymal disease in cases with pulmonary hypertension did not appear to be greater than in those without pulmonary hypertension.

Other workers have sought to account for the increased vascular resistance in mitral stenosis on the basis of structural changes in the pulmonary arteries. Edwards (1953) considered that the histological appearances of hypertensive pulmonary vascular disease suggested a persistence of the fœtal state of the small pulmonary arteries with subsequent elevation of the blood pressure giving rise to additional arterial changes.

The present investigation has demonstrated that pulmonary hypertension in mitral stenosis is invariably associated with a considerable reduction in the pulmonary arterial bed by structural changes that affect the arterioles and small pulmonary arteries throughout the lungs. These changes are of two kinds. First, the vessels are constricted and indistensible, and secondly they are the seat of intimal proliferation. Any theory that purports to nominate the cause of pulmonary hypertension in mitral stenosis must explain the origin of these structural changes.

The refractory arterial contraction which has in the past been mistaken for hypertrophy of the muscular arteries and muscularization of the arterioles, may be the result of long-continued arterial spasm. If, as Wood (1952) has suggested, these patients react abnormally to a rise in pulmonary arterial pressure by developing vaso-constriction, it is conceivable that this effect may lead ultimately to persistent arterial narrowing.

In regard to the nature and cause of the intimal proliferation, Thomas *et al.* (1956), failing to find significant correlation between moderate or advanced pulmonary arteriosclerosis and the presence of right ventricular hypertrophy, suggested that the degree of the arterial changes was insufficient to cause a significant increase in the pulmonary vascular resistance. They also concluded that thrombo-embolism was an important factor in the pathogenesis of the abnormal arterial changes. The authors, however, did not give details of the number of histological sections examined in each case nor of the site from which they had been taken; it is possible that sometimes they were not representative of the lungs as a whole.

In 1951 Evans postulated that most forms of pulmonary hypertension start with the presence of congenital deficiencies in the media of the lesser pulmonary arteries. In the presence of a raised pulmonary arterial pressure from any cause, intimal proliferation formed in connection with such deficiencies gives rise to arterial stenosis or occlusion and to pulmonary hypertension.

In a case of so-called primary pulmonary hypertension, Gilmour and Evans (1946) found innumerable foci of medial hypoplasia or aplasia. Similar foci were present in 9 of the 11 cases of solitary pulmonary hypertension reported by Evans *et al.* (1957), and in each of the 12 cases of pulmonary hypertension associated with mitral stenosis described in this paper. This mechanism would explain the more frequent finding of pulmonary hypertension in mitral stenosis than in other conditions, for the considerable rise in pulmonary arterial pressure consequent on the valvular block, acts as a powerful stimulus to the development of intimal proliferation, even in patients in whom medial deficiencies are not abundant.

Summary and Conclusions

The pulmonary vasculature was specially examined at necropsy in 24 patients with mitral stenosis in order to explain the presence of pulmonary hypertension in some and its absence in others.

The pulmonary arteriogram showed two kinds of abnormality, focal and diffuse. The focal changes were common to all cases, but the diffuse changes were only found in those in whom subsequent examination revealed severe arterial disease.

Histological examination likewise showed two kinds of abnormality, subsidiary and salient. The subsidiary changes, which included intimal thickening and thrombosis within the large arteries and subintimal thickening of the venules, were common to all cases. The salient changes, on the other hand, were confined to 12 cases, and consisted of two processes which together led to great narrowing of the arterial bed throughout the lung. First, there was diffuse refractory arterial and arteriolar contraction. Secondly, there was great and widespread intimal proliferation, in which thrombosis with subsequent organization may have played a part, within the arterioles and the muscular arteries under 0·2 mm. in diameter. Associated with the intimal proliferation in the small muscular arteries, there was hypoplasia of the media.

These salient changes were neither related to the degree of mitral stenosis, nor to the age of the patient, but in each of the twelve in whom they were present, there was great hypertrophy of the right ventricle at necropsy. Pulmonary hypertension was diagnosed in these patients during life on the basis of clinical, electrocardiographic, and radiological examination, and without recourse to pulmonary arterial catheterization.

This investigation, therefore, has established that vascular obstruction accounts for persistent pulmonary hypertension in mitral stenosis.

We believe that mitral valvotomy in these cases is unlikely to produce material or lasting benefit, for the arterial changes that they show appear to be progressive and irreversible. If surgery is undertaken, special care is necessary during anæsthesia and the operation.

We are indebted to Dr. D. Evan Bedford for permission to include three of his cases. Dr. Wallace Brigden has helped us with advice, and so has Dr. J. P. D. Mounsey. Professor Dorothy Russell has made available to us the findings at necropsy in many of the cases we describe here.

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John Reinhold's valuable work on heart sounds and murmurs in children will be known to many readers. He had recently obtained a post as Assistant Professor of Pædiatrics at Denver, Colorado, and was looking forward to his new opportunities. We deeply regret to record his death at the early age of 34, on July 19, 1957, as a result of injuries in a motor accident there.

RELATION OF THE FIRST AND SECOND HEART SOUNDS TO EVENTS IN THE CARDIAC CYCLE

BY

JOHN REINHOLD AND ULF RUDHE

From the Department of Child Health, Guy's Hospital, the Hospital for Sick Children, Great Ormond Street, London, and the Karolinska Sjukhuset, Stockholm

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" The chief value of the recorded heart sound is the possibility of accurately timing its occurrence in relation to the events of the cardiac cycle." This is even truer to-day than when Lewis first stated it (1915), because methods for recording events in the cardiac cycle have become more precise. In spite of this, there is still lack of agreement on the origin of the heart sounds. The causes of the second heart sound have been clearly defined, but there is a divergence of opinion on the origin of the major components of the first heart sound. On auscultation in young people the first sound may be heard to be narrowly split at the lower left sternal border. This splitting is widest and therefore most easily heard at the end of expiration (Potain, 1866). The origin of these two components has been attributed by some to closure of the auriculo-ventricular valves followed by opening of the semilunar valves (Orias and Braun-Menendez, 1939; Rappaport and Sprague, 1942; Luisada *et al.*, 1949; Nazzi *et al.*, 1954). Others have suggested that it is due to asynchronism in contraction of the ventricles (Wolferth and Margolies, 1945), and so to closure of the mitral valve followed by closure of the tricuspid valve (Leatham, 1954). Much of the evidence for these views has been obtained by relating the components of the heart sounds to dynamic events in the cardiac cycle by the use of reference tracings. Phlebograms and indirect carotid artery tracings have been mainly used for this purpose but these have the disadvantage that an arbitrary time interval has to be allowed for pulse wave transmission when assessing results.

The present investigation has been undertaken to study the nature of the first and second heart sounds and to relate their components to events in the cardiac cycle by the use of synchronous border electrokymograms. These tracings represent volume and positional changes of the heart chambers and the great vessels during the cardiac cycle. Positive waves indicate outward movement and negative waves indicate inward movement of the heart borders. These tracings have the advantage of eliminating the arbitrary time factor for pulse wave transmission.

METHODS

In the first part of the investigation phonocardiograms were taken, using the Elmqvist six-channel Klinik recorder, with three different frequency responses. These are designated high frequency, medium frequency, and low frequency according to the degree of attenuation of low frequency vibrations in each; the high and medium frequency tracings are similar to the logarithmic phonocardiogram of Rappaport and Sprague (1942) in their frequency response. Within the range of the heart sounds and murmurs the medium frequency channel has a pattern in its frequency response similar to the human audiogram; it thus represents the heart sounds as they are heard through the stethoscope. The low frequency tracings represent rather lower frequencies than are ordinarily heard through a stethoscope. Recordings were taken routinely from the apex, the fourth and second left intercostal spaces, and the second right intercostal space. Reference tracings

were provided by lead II electrocardiograms, phlebograms, and carotid artery tracings recorded from the suprasternal notch; in some cases apex cardiograms also were recorded. Phlebograms and carotid tracings were obtained indirectly with a metal stylus resting over the vessel, impulses being transmitted directly to a crystal of Rochelle salt, and the voltage produced being amplified and subsequently recorded by a mirror galvanometer. It has been shown previously that there is no electrical delay in this circuit (Reinhold *et al.*, 1955).

In the major part of this investigation medium frequency phonocardiograms were taken synchronously with border electrokymograms, lead II electrocardiograms and apex-cardiograms. Phonocardiograms were recorded from the four standard sites. Electrokymograms were taken from the base of the ascending aorta approximately 4–5 cm. above the aortic valve, from the pulmonary artery close to the pulmonary valve, from the left and right auricles, and in many cases from the apices of the left and right ventricles. Recordings were also made from the aortic arch in a few patients. The majority of recordings were taken with the patient in the erect position. The electrical delay in the electrokymogram circuit compared with that of the phonocardiogram was slightly less than 0·01 sec. This was estimated by feeding an electric signal to the inputs of the electrocardiogram, apex-cardiogram, phonocardiogram, and electrokymogram amplifiers. The response of each was recorded simultaneously and showed no time lag between the electrocardiogram, apex-cardiogram and phonocardiogram, and slightly less than 0·01 sec. lag of the electrokymogram behind these three tracings. Consequently, an allowance of 0·01 sec. has been made in all tracings for this delay.

Interpretation of the Normal Electrokymogram

Aotric valve opening was denoted by the point of upstroke of the electrokymogram recorded from the ascending aorta, no time allowance being necessary for pulse wave transmission. In some instances there was a small positive wave (Fig. 1A) or an inflexion (Fig. 1B) preceding the main

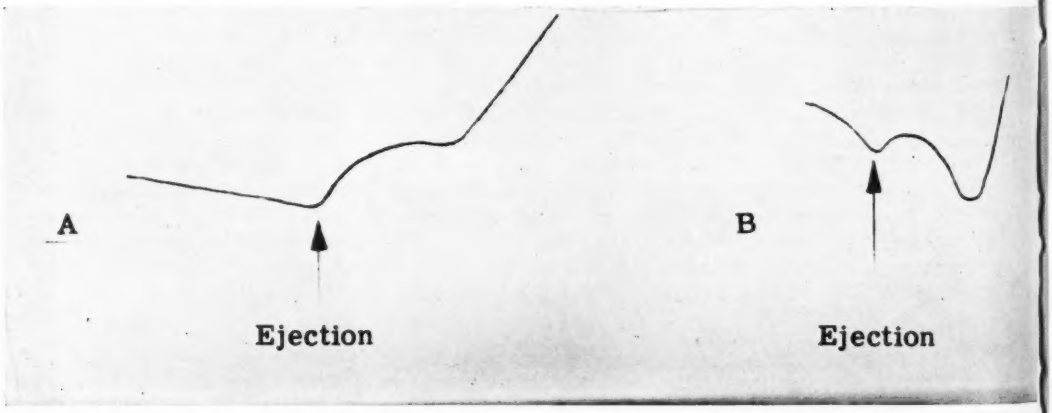

Fig. 1.—Electrokymogram from ascending aorta (see text).

upstroke. By comparison with left ventricular and aortic arch tracings it was apparent that the onset of ejection into the aorta was denoted by the first rise on these tracings (↑). The cause for this distortion of the ejection wave is probably the brisk downward movement of the base of the heart that occurs at the beginning of the isotonic phase of ventricular systole (Luisada, 1953). *Aotric valve closure* was denoted by the dicrotic notch on the same tracing.

Pulmonary valve opening was denoted by the point of upstroke of the pulmonary artery electro-

kymogram, no time allowance for pulse wave transmission being necessary because the tracings were recorded from the artery immediately beyond the valve. *Pulmonary valve closure* was denoted by the dicrotic notch on this electrokymogram.

The point that was considered to be synchronous with *mitral valve closure* was determined from a typical inflexion on the left auricular electrokymogram. It has been stated by Braunwald *et al.* (1955) that mitral valve closure is virtually simultaneous with the onset of isometric left ventricular contraction. The end of auricular contraction (A_2) and the beginning of the isometric ventricular phase on the left auricular electrokymogram (S_1) are often simultaneous and are marked by the onset of a positive wave following the negative auricular systolic wave (Mednick *et al.*, 1950; Rudhe, 1956). This point has been taken as indicating the time of mitral valve closure. On the right auricular electrokymogram, there is often a brief interval between the end of auricular systole and the onset of isometric right ventricular contraction. This is usually denoted by a slight rise in gradient of the tracing after A_2 followed by a sharp inflexion (S_1), which is in turn succeeded by a steeper rise to S_2 (Fig. 2). Although S_1 is not always present on this tracing, we have confined our observations to those records in which this inflexion is clearly visible.

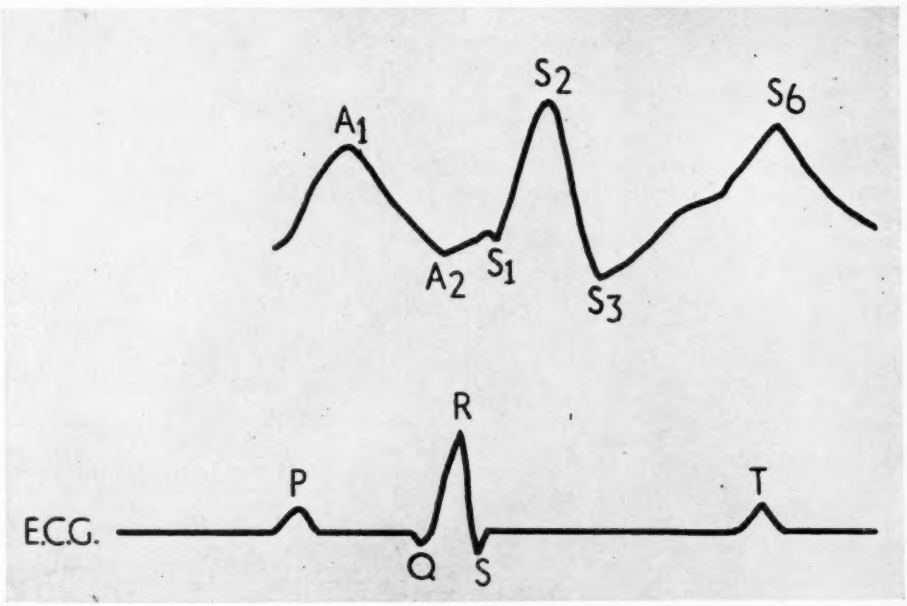

FIG. 2.—Electrokymogram from right auricle.

It is generally believed that this point denotes the onset of isometric right ventricular systole (Booth *et al.*, 1953; Rudhe, 1956), and is therefore synchronous with *closure of the tricuspid valve* These points of reference have been checked by comparison with right and left ventricular electrokymograms where the onset of isometric contraction is denoted by a preliminary downward inflexion before the main ejection wave (Mednick *et al.*, 1950).

It is generally agreed that *opening of the mitral and tricuspid valves* is marked by the point where the auricular diastolic wave ends (S_6) and where there is a sharp fall in the curve with the onset of the first rapid phase of ventricular filling. It has been shown that this point corresponds

closely to the fall in pressure on the right auricular pressure curve at the end of auricular diastole (Rudhe, 1956).

Material

Forty-five normal children and young adults were included in the investigation. Twenty were investigated with the aid of electrokymograms but in only sixteen were the points on the auricular tracings defined clearly enough for analysis of their relationship to the first heart sound. The remaining subjects were examined with carotid or jugular reference tracings. One patient with complete heart block was included to study the relationship of the time of auricular systole to the amplitude of the components of the first heart sound.

Results

In many subjects, careful auscultation revealed splitting of the first heart sound, best heard at the lower left sternal border. In all subjects splitting of the second heart sound was heard at the pulmonary area.

The First Sound

In many previous studies the first sound has been divided into four components (Orias and Braun-Menendez, 1939; Rappaport and Sprague, 1942; Nazzi *et al.*, 1954). Of these the second and third are the audible major components.

In 33 normal subjects studied by phonocardiography it has been possible to separate the first sound into these four components in all instances. In this work these have been called the initial component, the first and second major components and the final component. The major components, which give the impression of splitting on auscultation, were best recorded at the lower left sternal border although they were also often well registered at the apex. The duration of the first sound and of its individual components has been measured in each subject on the medium frequency tracing at the apex, and the site of maximum registration of each component has been recorded (Table I). We have made no attempt to record the number of vibrations making up each component as this varies with the method of recording (Mannheimer, 1955). Neither have we attempted to measure the frequency of each component because the first heart sound, being composed of a conglomeration of unrelated frequencies, cannot be regarded as a pure harmonic vibration. Moreover, the vibrational frequencies of the heart sounds vary with the frequency response of the apparatus and the type of chest piece employed (Rappaport and Sprague, 1942). However, we have attempted to determine whether one component contained more higher frequency vibrations than another in the medium frequency channel.

TABLE I

THE AVERAGE DURATION AND THE SITE OF MAXIMUM REGISTRATION OF THE 1ST SOUND IN 33 NORMAL SUBJECTS (Medium Frequency Channel)

	Initial component	1st major component	2nd major component	Final component
Site of maximum registration	Apex	Apex	4. L.I.S.	Base
Duration (sec.)	0·04	0·03	0·02	0·04
(Range)	(0·02–0·05)	(0·02–0·04)	(0·01–0·04)	(0·01–0·07)
Total duration of 1st sound. (sec.) ..	0·13 (0·09–0·15)			

The initial component was of lower amplitude than the first and second major components in all areas and was best registered at the apex. In the majority of subjects it was not registered over the

base of the heart. It appeared to be mainly composed of low frequency vibrations. By means of the synchronous left auricular electrokymogram it was shown that this component occurred in the pre-isometric phase immediately before the onset of isometric left ventricular contraction.

The first major component was registered in all areas, but best at the apex. It was of considerably greater amplitude than the initial component and, in many subjects, it was of slightly greater amplitude than the second major component at the apex. Both major components appeared to contain more high frequency vibrations than the initial and final components.

By comparison with the left auricular electrokymogram (Fig. 3), the onset of the first major component was correlated with the onset of left ventricular isometric contraction and the time of mitral valve closure (Table II). The two events were synchronous in 11 out of 16 instances, and

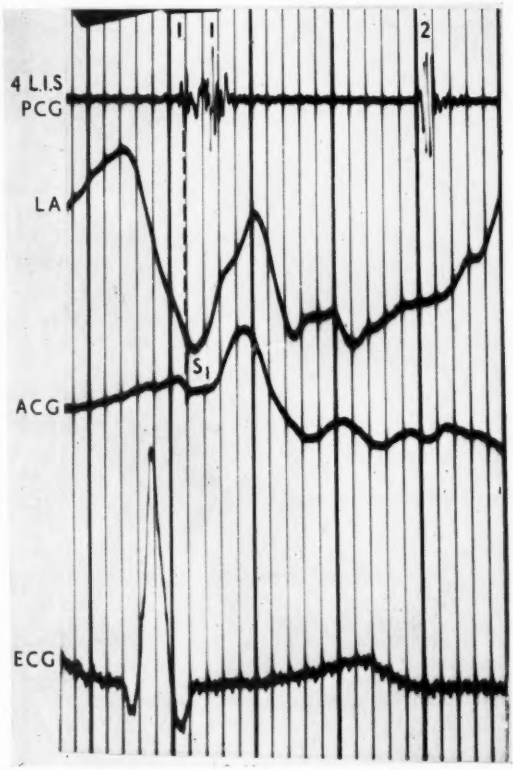

FIG. 3.—Synchronous medium frequency phonocardiogram (PCG) and left auricular electrokymogram (LA) in a normal child, showing relationship of onset of left ventricular isometric contraction (S_1) to the first major component of the first sound. (Enlarged ×2.) 4 L.I.S.=Fourth left intercostal space. ACG=apex-cardiogram. ECG=electrocardiogram. Time intervals 0·02 and 0·1 sec. 0·01 sec. delay on electrokymogram has been allowed for in this and all subsequent tracings.

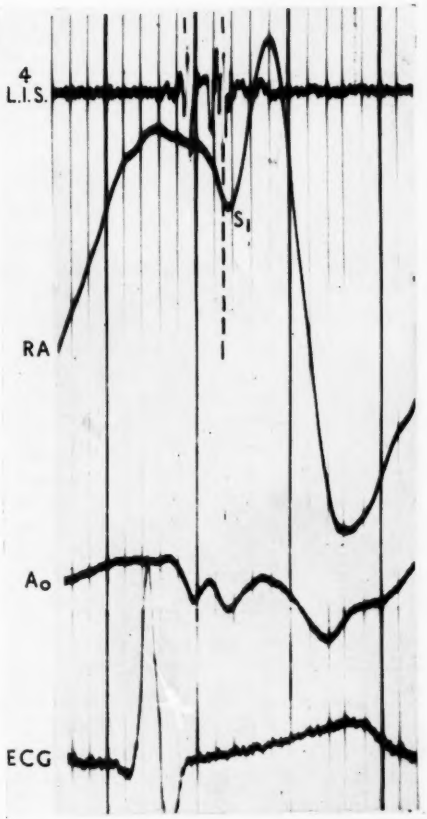

FIG. 4.—Synchronous medium frequency phonocardiogram and right auricular electrokymogram (RA) in a normal child, showing relationship of onset of right ventricular isometric contraction (S_1) to the second major component of the first sound. (Enlarged ×2.)
Note. Ao should be ACG, apex-cardiogram.

TABLE II

THE RELATION OF THE COMPONENTS OF THE 1ST SOUND TO EVENTS IN THE CARDIAC CYCLE IN NORMAL SUBJECTS DEFINED BY SYNCHRONOUS ELECTROKYMOGRAMS

Interval	Average duration in sec. (range)	No. of observations
Q—Initial component	0·04 (0·02–0·05)	17
Q—1st major component	0·07 (0·05–0·09)	16
Q—Onset of L.V. isometric phase. (Mitral valve closure)	0·08 (0·05–0·09)	16
Q—2nd major component	0·10 (0·08–0·13)	16
Q—Onset of R.V. isometric phase. (Tricuspid valve closure)	0·10 (0·07–0·13)	16
Q—Final component	0·12 (0·10–0·16)	17
Q—Aortic valve opening	0·11 (0·08–0·15)	17
Q—Pulmonary valve opening	0·13 (0·07–0·17)	17

0·01 sec. has been subtracted for electrical delay in the electrokymograph circuit.

the first major component preceded aortic and pulmonary valve opening by an average of 0·04 and 0·05 sec. respectively.

The second major component was registered in all areas, but best at the fourth left intercostal space, where, in most subjects, it was of greater amplitude than the first major component. It followed the first major component by an average interval of 0·03 sec.

By means of the right auricular electrokymogram, the second major component was shown to be synchronous with the notch on this tracing (S_1) indicating the onset of isometric right ventricular systole and tricuspid valve closure in 12 out of 16 instances (Fig. 4). The second major component preceded aortic (Fig. 5) and pulmonary valve opening (Fig. 6) in nearly all subjects (Table II).

The final component was registered in all areas but best over the base of the heart at the second left and second right intercostal spaces; in a few instances it was best recorded at the apex. These vibrations occurred at the time of or immediately after the opening of the aortic and pulmonary valves (Fig. 5 and 6), and were of lower amplitude than the major components and contained a preponderance of lower frequency vibrations.

The Effect of Auricular Contraction on the Amplitude of the First Heart Sound

It is known that the intensity of the first heart sound varies with the P–R interval, the sound being louder when the interval is short and softer when it is long (Griffith, 1911–12; Lewis, 1915). This is probably due to the effect of auricular contraction upon the position of the auriculo-ventricular valves. If the P–R interval is long the valves have time to float upwards towards the position of closure before isometric ventricular systole begins and finally causes them to close. Therefore they will give rise to a soft sound on closing. If the P–R interval is short, the onset of the isometric phase occurs before auricular systole has ended and the auriculo-ventricular valves are still wide open and so come together with a loud snap (Wolferth and Margolies, 1930). In the light of this interpretation, if the two major components of the first sound are related to mitral and tricuspid valve closure, one might expect that they would vary in amplitude independently of each other and according to their individual time relationship with auricular systole. This phenomenon has indeed been demonstrated in two cases of complete heart block by Wolferth and Margolies

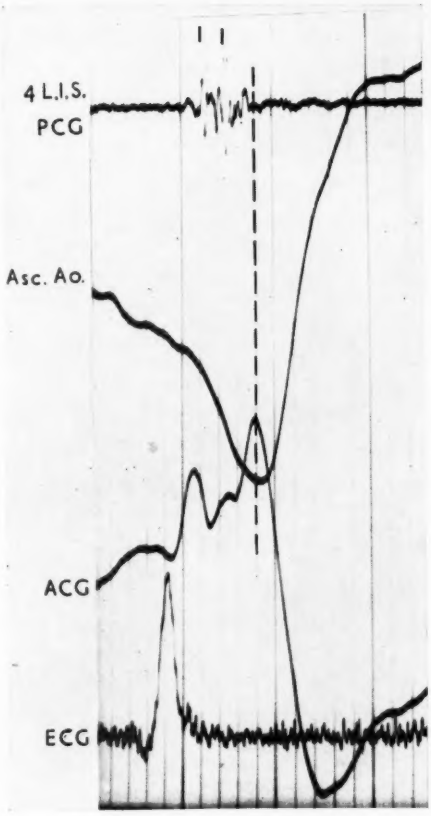

FIG. 5.—Synchronous medium frequency phonocardiogram and electrokymogram from base of ascending aorta (Asc. Ao.), showing that the major components of the first sound occur before aortic valve opening and the onset of systolic ejection into the aorta. (Enlarged ×2.)

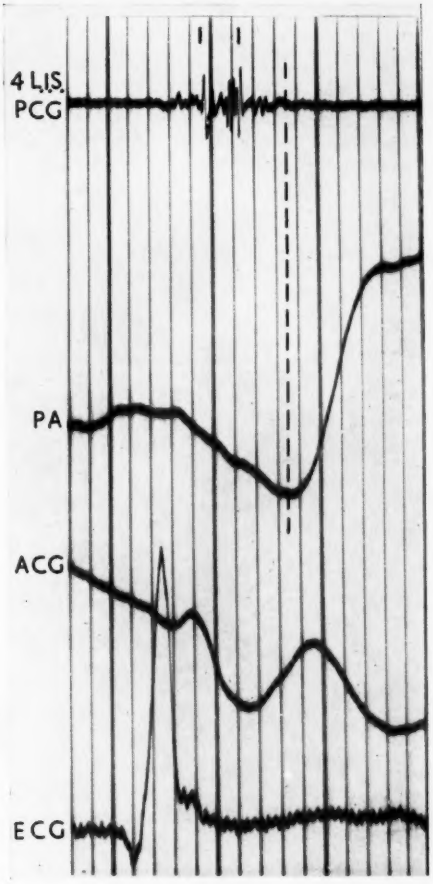

FIG. 6.—Synchronous medium frequency phonocardiogram and electrokymogram from the base of the pulmonary artery (PA), showing that the major components of the first sound occur before pulmonary valve opening and the onset of systolic ejection into the pulmonary artery. (Enlarged ×2.)

(1935). They showed that each component of the first heart sound had its own clear-cut relationship to the P wave by measuring the interval between the onset of P and the individual components in each complex. They also found that the time zone of intervals between P waves and sound components during which sound vibrations of large and small amplitude were recorded, differed very little for the two components. From this they deduced that the amplitude of the two components was dependent on the different auriculo-ventricular intervals on the two sides of the heart. They pointed out, however, that their investigation would have been greatly simplified if they had been able to measure the auriculo-ventricular intervals on the two sides by other than electrocardiographic methods.

With the aid of electrokymography we have had the opportunity of studying the relationship of

left and right auricular systole to the amplitude of the major components of the first heart sound in one patient with complete heart block. In Table III the time interval between the onset of left and right auricular systole and the first and second components of the first sound has been compared with their amplitude from cycle to cycle. Although the onset of auricular systole on the electrokymogram is later than that obtained by auricular pressure recordings (Rudhe, 1956), there appears to be a comparable time range for the two sides of the heart when the amplitude of the appropriate sound component is greater (Table III).

TABLE III

THE RELATIONSHIP OF THE P–R INTERVAL AND OF THE TIME OF AURICULAR CONTRACTION, MEASURED ON THE ELECTROKYMOGRAM, TO THE AMPLITUDE OF THE FIRST HEART SOUND COMPONENTS

Time interval		Max. amp. of 1st component (mm.)	Time interval		Max. amp. of 2nd component (mm.)
P–R (sec.)	A_1 (Lt. auricle) to 1st component (sec.)		P–R or R–P (sec.)	A_1 (Rt. auricle) to 2nd component (sec.)	
0·02	0·01	5	R–P	2–A_1	
0·04	0·04	8	0·07	0·06	12
0·10	*0·06*	30			
0·12	*0·08*	24	P–R	A_1–2	
0·14	*0·08*	22	*0·06*	*0·04*	30
0·14	*0·11*	19	*0·06*	*0·05*	34
0·18	0·15	5	*0·08*	*0·06*	38
0·21	0·19	3	*0·08*	*0·08*	36
0·24	0·21	4	*0·11*	*0·10*	28
0·30	0·29	5	*0·11*	*0·10*	26
0·34	0·30	8	0·13	0·12	12
			0·26	0·24	4
			0·32	0·30	5
			0·33	0·32	8

On the left side, when the auricle begins to contract (as estimated by the electrokymogram) 0·06–0·11 sec. before the first component, the latter is increased in amplitude; but earlier or later contraction of this auricle is associated with much lower amplitude of the first component. On the right side, when the onset of auricular contraction (similarly estimated) is 0·04–0·10 sec. before the second component, the amplitude of the sound is increased. Earlier or later contraction of the auricle is associated with lower amplitude of the second component. This relationship of auricular contraction and of the P–R interval to the amplitude of the first sound components is seen in Fig. 8. In beat 1 the auricles contract too early to affect either component; in beat 2 the auricles contract nearer to the first sound so that both components are affected, but the first is of greater amplitude than the second. In beat 3 both components are equally increased in amplitude by their relationship to auricular contraction and in subsequent beats the auricle is contracting too close to the first sound to affect the first component, but the second is accentuated. These findings confirm those of Wolferth and Margolies and support their postulate that the two major components of the first heart sound are due to similar events occurring asynchronously in opposite sides of the heart.

The Second Sound

For a long time it has been believed that the major components of the second heart sound are due to closure of the semilunar valves (Carswell, 1832; Billing, 1832; Rouanet, 1832). Splitting of the second sound in the pulmonary area is well recognized as a normal phenomenon, and it is known that this splitting increases with inspiration, and diminishes with expiration (Potain, 1866). The first component has been shown to be due to aortic valve closure by its relationship to the dicrotic

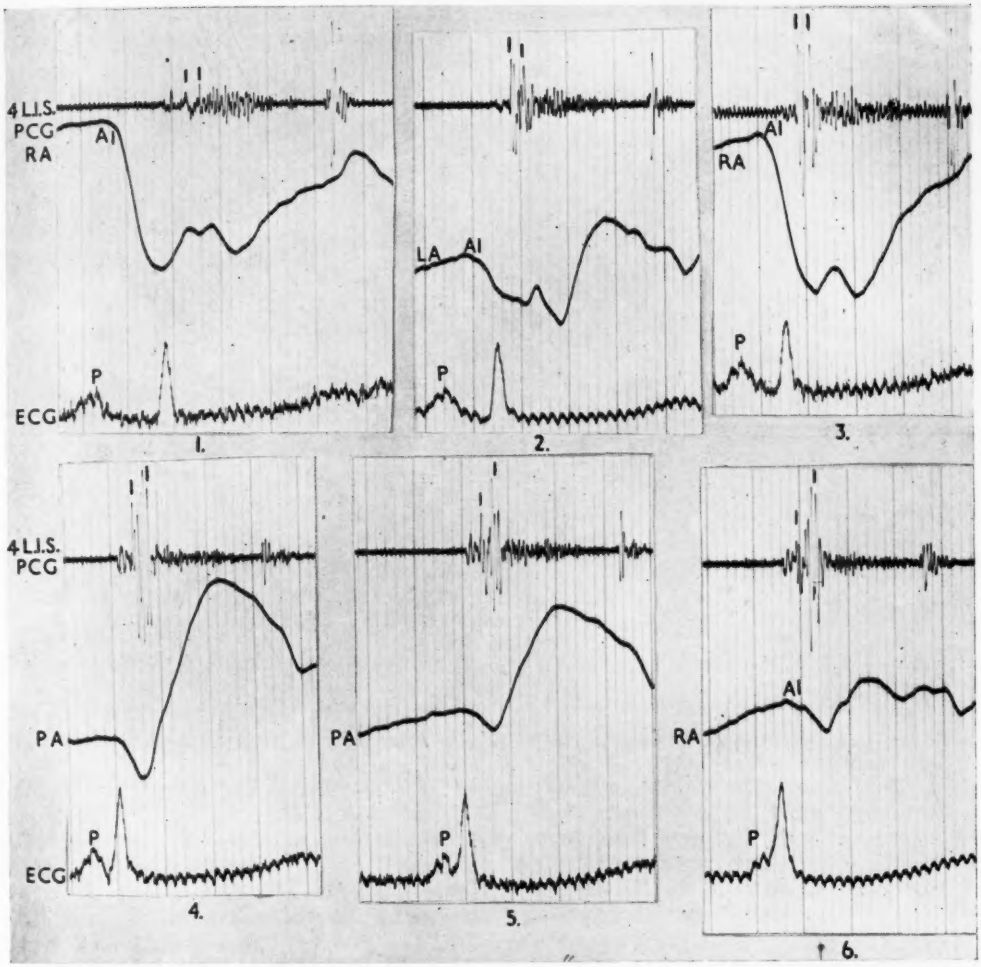

FIG. 7.—Synchronous medium frequency phonocardiograms, electrocardiograms, and electrokymograms from left auricle (LA), right auricle (RA) and pulmonary artery (PA) in a child with complete heart block. The individual tracings show the relationship between the amplitude of the major components of the first heart sound, the time of onset of auricular systole on the electrokymogram and the P–R interval.

notch of the carotid tracing and it alone is responsible for the second sound at the aortic area and the apex. The second component, being maximal at the second left intercostal space, has been thought to be due to pulmonary valve closure (Leatham, 1954). It has also been suggested that small low frequency vibrations following the major component at the apex are due to opening of the auriculo-ventricular valves (Rappaport and Sprague, 1942).

Analysis of the phonocardiogram in 45 normal young people showed the major component of the second sound to be single at the apex and second right intercostal spaces and split at the second left intercostal space in all instances. The second major component of the second sound was also recorded at the fourth left intercostal space, but with diminished amplitude. At the apex and

the fourth left intercostal space, a few low amplitude vibrations of short duration were recorded after the major component; these were best seen on the low-frequency tracing. The characteristics of the second sound and its relationship to events in the cardiac cycle are shown in Table IV.

Splitting of the second sound varied with respiration and was greatest on inspiration, and often disappeared at the end of expiration.

The first major component was timed against the dicrotic notch on the electrokymogram taken from the ascending aorta, and was shown to precede it in all instances by an average interval of

TABLE IV

CHARACTERISTICS OF THE SECOND SOUND AND ITS RELATION TO EVENTS IN THE CARDIAC CYCLE BY REFERENCE TO SYNCHRONOUS ELECTROKYMOGRAMS

Interval	Average duration in sec. (range)	No. of observations
Separation of 1st and 2nd components (mid-respiration)	0·05 (0·03–0·07)	45
1st component—Aortic dicrotic notch	0·03 (0·02–0·03)	20
Aortic dicrotic notch—2nd component	0·02 (0·01–0·05)	21
2nd component—Pulm. dicrotic notch	0·02 (0·01–0·03)	20
Max. duration 2nd sound (Apex or 4 L.I.S.) ..	0·08 (0·06–0·10)	21
Onset 2nd sound—Tricuspid valve opening ..	0·07 (0·04–0·10)	21
Onset 2nd sound—Mitral valve opening	0·10 (0·04–0·14)	20
Comparative amplitude of 1st to 2nd component at 2 L.I.S.	1·5 : 1 (0·9–5·0 : 1)	37

0·03 sec. (Fig. 8). It preceded the dicrotic notch on the pulmonary artery electrokymogram by an average of 0·07 sec.

The second major component occurred after the aortic dicrotic notch in all instances (Fig. 8) and thus could not be due to aortic valve closure. It preceded the dicrotic notch on the pulmonary artery electrokymogram (Fig. 9) indicating its relationship to pulmonary valve closure. It will be seen from Table IV that there was a short delay of the aortic dicrotic notch after the first component and of the pulmonary dicrotic notch after the second component. It seems unlikely that this delay is due to pulse wave transmission as the electrokymograms were taken from points on the aorta and pulmonary artery close to the semilunar valves; it is probable that it is accounted for by positional changes of the arteries at the time of valve closure (Rudhe, 1956).

The terminal low amplitude vibrations on the medium frequency tracing were related to opening of the mitral and tricuspid valves by reference to the left and right auricular electrokymograms (Table IV). The tricuspid valve opened shortly before the mitral valve in 17 instances and soon after the mitral valve in 2 instances; in one both valves opened simultaneously. Tricuspid valve opening was synchronous with the terminal vibrations of the second sound in 16 subjects and occurred after these vibrations in 5. Mitral valve opening was synchronous with these vibrations in 6 subjects and occurred after them in 14.

DISCUSSION

The First Heart Sound

The vibrations that constitute the first heart sound have been attributed by different authors to muscular, vascular, and valvular events in the cardiac cycle. For some time, the initial vibrations were thought to be due to auricular factors (Bramwell, 1935; Cossio and Lascales, 1936; Orias and Braun-Menendez, 1939; Rappaport and Sprague, 1942); but it is now believed that the auricle plays no part in the production of the first sound (Wiggers and Dean, 1917; Lian *et al.*, 1941;

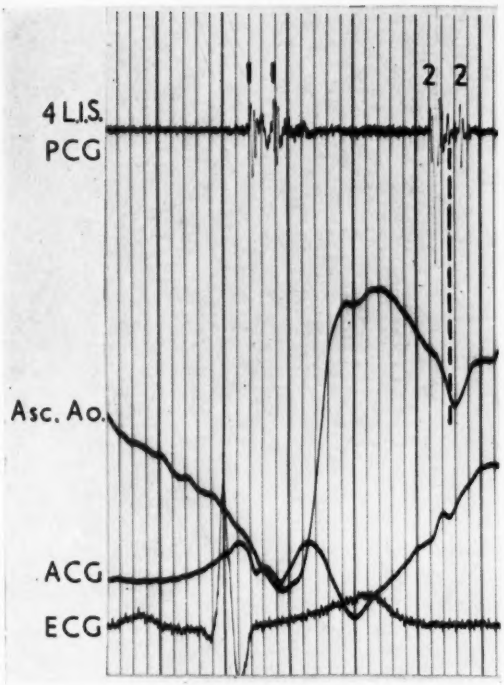

FIG. 8.—Synchronous medium frequency phonocardiogram and electrokymograms from the base of the ascending aorta (Asc. Ao.) in a normal child, showing the relationship of the aortic dicrotic notch to the major components of the split second sound.

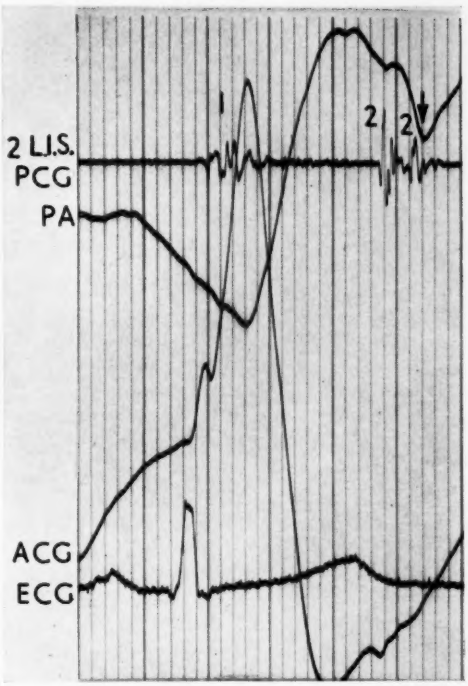

FIG. 9.—Synchronous medium frequency phonocardiograms and electrokymograms from the base of the pulmonary artery in a normal child, showing the relationship of the pulmonary dicrotic notch to the second major component of the split second sound. 2 L.I.S.=Second left intercostal space.

Counihan *et al.*, 1951), and that the initial vibrations, occurring in the pre-isometric phase of ventricular systole, are caused by muscular factors due to changes in the shape of the ventricle immediately prior to the onset of isometric contraction (Nazzi *et al.*, 1954).

There is general agreement that the onset of the first major component occurs approximately at the time of isometric ventricular contraction (Wiggers and Dean, 1917; Orias and Braun-Menendez, 1939; Rappaport and Sprague, 1942; Wolferth and Margolies, 1945; Leatham and Vogelpoel, 1954; Nazzi *et al.*, 1954). There is much less agreement on the relationship of the second major component to the isometric and the ejection phases of systole. Some have stated that this component is related to the onset of systolic ejection and is either due to vibration of the valve cusps before they open (Geigel, 1906), or to the actual opening of the valves (Einthoven and Geluk, 1894). Others believe that systolic ejection and semilunar valve opening do not contribute to the major components, and that auriculo-ventricular valve closure is mainly responsible for the production of the first heart sound (Rouanet, 1832; Dock, 1933). Recently Leatham (1954) has suggested that the major components of this sound are due to asynchronous mitral and tricuspid valve closure and he has pointed out that the first component is louder at the apex and the second at the lower left sternal border. Wolferth and Margolies (1945) support the idea that splitting of the first heart sound is due to asynchronism of ventricular contraction, and Katz (1925) has shown that slight asynchronism of ventricular contraction is present in the dog's heart. This finding has been confirmed in man by electrokymographic studies (Mednick *et al.*, 1950), left ventricular

ejection preceding right ventricular ejection in most instances (Hamilton *et al.*, 1947; Ellinger *et al.*, 1948).

Our observations have confirmed that there is normally some asynchronism of isometric ventricular contraction and of systolic ejection, and that the left precedes the right. They have also shown that, in the majority of subjects, the onset of left ventricular isometric contraction coincides with the first major component and that of right ventricular isometric contraction with the second major component of the first sound. It is generally believed that the auriculo-ventricular valves begin to close towards the end of auricular systole and that closure takes place simultaneously with the onset of isometric ventricular systole (Dean, 1916; Leatham and Vogelpoel, 1954; Braunwald *et al.*, 1955). Therefore it seems reasonable to conclude that the first major component of the first sound is due to mitral valve closure and the second major component to tricuspid valve closure.

The observation that the amplitude of each component varies individually with its relationship to the time of onset of left and right auricular systole provides further supportive evidence for the suggestion that both components are due to similar events occurring on opposite sides of the heart. It would be difficult to account for the variation in amplitude of the second component relative to the time of auricular systole if one attributed its origin to semilunar valve opening. Moreover, aortic and pulmonary valve opening, timed by the electrokymogram, usually followed after the second major component. It is unlikely, therefore, that these events bear any relation to this sound. They were, however, related to the final component of the first heart sound the vibrations of which were best registered over the base of the heart and often continued for a short time after the onset of systolic ejection. It seems more probable that these vibrations are due to ejection of blood into the great vessels rather than to semilunar valve opening.

The second sound in young people is normally single on auscultation at the apex and second right intercostal space and split at the second left intercostal space. This also has been attributed to asynchronism of ventricular contraction. The first part, which is that heard at the apex and second right space, is due to aortic valve closure and it is believed that the second part is due to pulmonary valve closure (Abrahams and Wood, 1951; Leatham, 1952, 1954). Our observations support this belief by showing that the first part is closely related to the aortic dicrotic notch and the second to the pulmonary dicrotic notch on the electrokymogram. Increase in splitting of the second sound with inspiration is due to delayed closure of the pulmonary valve (Leatham and Towers, 1951) which in turn is probably due to overfilling of the right ventricle and prolongation of right ventricular systole.

The peak of the right auricular filling wave on the electrokymogram is known to correspond to the peak of the V wave on the right auricular pressure tracing (Rudhe, 1956), and it is therefore synchronous with tricuspid valve opening. There was a close relationship between the terminal vibrations of the second sound and tricuspid valve opening timed in this manner. Mitral valve opening, timed by the left auricular electrokymogram, appeared to occur after the final vibrations of the second sound in many instances. It is probable, however, that the terminal vibrations of the second sound were not always registered on the medium frequency phonocardiogram owing to attenuation of low frequencies in this channel. Therefore, it is concluded that the final vibrations of the second sound are probably related to opening of the auriculo-ventricular valves; but, because of their low amplitude and low frequencies in normal subjects, they are not audible on auscultation.

Conclusions

The first and second heart sounds are often audibly split in normal young people. Splitting of the first sound is most clearly heard at the lower left sternal border at the end of expiration, and of the second sound at the second left intercostal space at the height of inspiration.

The modern concept of the ætiology of the major components of the first and second heart sounds (Leatham, 1954) has been substantiated by their investigation with the aid of electrokymography. The two major components of the first sound that contribute to the splitting are separated

by an average interval of 0·03 sec. and are of greater amplitude and contain more high-frequency vibrations than the other components. In most instances the first major component is synchronous with the onset of left ventricular isometric contraction and the second with the onset of right ventricular isometric contraction timed by the auricular electrokymogram. From this observation, it is concluded that the first major component is due to closure of the mitral valve and the second to closure of the tricuspid valve. Observations on the amplitude of each component relative to left and right auricular systole support this hypothesis. Semilunar valve opening, both aortic and pulmonary, occurs after the second major component in most cases; therefore, it is unlikely that this event has any relation to the audible components of the first heart sound.

Comparison of the aortic and pulmonary dicrotic notches with the two components of the split second sound has shown that the first is due to aortic valve closure and the second to pulmonary valve closure. They are separated by an average interval of 0·05 sec. in mid-respiration, but this increases during inspiration. Opening of the auriculo-ventricular valves does not contribute to the audible components of the second heart sound in normal people.

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HEART SOUNDS AND INTRACARDIAC PRESSURES IN MITRAL STENOSIS

BY

DESMOND JULIAN * AND L. G. DAVIES

From the National Heart Hospital and the Institute of Cardiology

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It has been thought for many years that, in the absence of conduction defects, the time of occurrence of the heart sounds is largely determined by intracardiac pressure and flow changes. It is convenient to examine this hypothesis in mitral stenosis, where the exact time of mitral valve opening and closure can be obtained from the phonocardiogram. This usually shows two abnormal features (Wells, 1954) in addition to the diastolic murmur. First there is often an increase of the time between the QRS of the electrocardiogram and the onset of the maximal vibrations of the first heart sound (Weiss and Joachim, 1911; Cossio and Berconsky, 1943). These vibrations arise in the mitral valve and this interval may be called R–M_1 if one measures from the onset of the intrinsicoid deflection as has been done in this study: other workers refer to a Q–M_1 interval, but for the purposes of measurement, we found the peak of R better than Q. Presumably, mitral valve closure is delayed by the raised pressure in the left atrium and there should be a relation between this pressure and the R–M_1: certainly as Kelly (1955) has pointed out, mitral stenosis is the only condition in which this interval is prolonged. One result of this delay is that the sound due to mitral valve closure becomes superimposed on that arising from tricuspid valve closure, and this effect contributes to the loud first sound in mitral stenosis.

The second abnormality is the presence of an added sound—the opening snap of the mitral valve—and since this is a left-sided event its time of occurrence is best measured from the instant of aortic valve closure. This measurement will be referred to as the A–OS interval and is the time taken for the left ventricular pressure to fall from that of aortic valve closure to the left atrial level—when the mitral valve opens. Again it seems reasonable to suppose that there should be a relation between this time and the left atrial pressure.

The suggestion that these two intervals were dependent on the pressure gradient across the mitral valve was made by Messer *et al.* (1951). Further work by Wells (1954) showed that the intervals could be correlated with the size of the mitral valve as measured at operation: this relationship must be indirect for the third variable, flow, was unknown; and his data are unsatisfactory in that he was unable to relate the time intervals with pressures recorded simultaneously. We have found important variations, particularly in the A–OS interval when comparing phonocardiograms taken at the time of cardiac catheterization and other times.

In this study the hypothesis relating sounds to pressures has been examined by correlating the R–M_1 and A–OS intervals with the coincident left atrial pressures. As already indicated we thought it essential that the phonocardiograms, electrocardiograms, and intracardiac pressures should be recorded simultaneously. We hoped that the intervals and pressures would in fact show a correlation close enough to predict the swing of left atrial pressure from measurement of the phonocardiogram; and further that this information could be used to estimate the degree of mitral valve obstruction without the necessity of cardiac catheterization, but this object was not

* Present address: Peter Bent Brigham Hospital, Boston, Mass.

achieved because, as will be seen, the left atrial pressure was sometimes found to be less important than other factors in determining the Q–M_1 interval.

METHODS

Synchronous tracings of intracardiac pressures, phonocardiograms, and electrocardiograms were obtained on a N.E.P. photographic recorder from 27 patients with mitral valve disease. A fast paper speed of 80 cm. a second was used to improve accuracy of measurement. The sternal angle was taken as the zero point of reference and the records were obtained during held expiration except where otherwise stated; Fig. 1, 2, and 3 illustrate the method in detail. The wedged pulmonary artery pressure was obtained at cardiac catheterization and we assumed that this is equivalent to the left atrial pressure pulse, though it

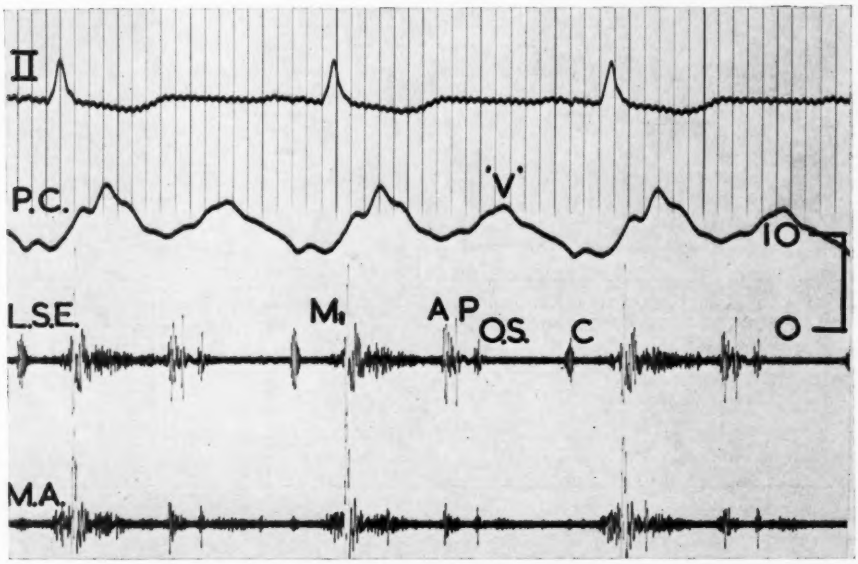

FIG. 1.—The method of obtaining the R–M_1 and A–OS intervals together with the synchronous "left atrial" pressure. The small time intervals are 0·04 sec. and the calibration is in mm. of mercury. The peak of *v* appears later than the opening snap because of a slight delay in the recording system. The peak of *a* is distorted by the first heart sound artefact probably due to the transmission through the catheter of the impact of tricuspid valve closure.

II—lead II of electrocardiogram	M_1	—mitral	valve closure
P.C.—wedged pulmonary artery tracing	A	—aortic	
L.S.E. } phonocardiograms at left sternal	P	—pulmonary	
M.A. } edge and mitral area	O.S.	—mitral opening snap	
	C	—artefact	

is not less than 0·02 sec. later (Epps and Adler, 1953). In addition the pressure record is further delayed by the instrumental lag in the catheter and manometer system. For this reason the *v* peak and the opening snap do not appear synchronous (Fig. 1). A further difficulty in the interpretation and measurement of the left atrial pressure pulse may arise as the result of artefacts occurring at the time of the first and second heart sounds (see Fig. 1, 2, and 3), artefacts that may be due to the transmission through the catheter of the impact of tricuspid and pulmonary valve closure. Because of these artefacts and further slight distortion due to the presence of *f* waves (Fig. 3), the peak of *v* may sometimes appear to precede the opening snap. This of course is impossible and the true pressure at *v* has to be measured a little after the snap (usually 0·04–0·08 sec.). *z* was taken as the nadir before the *c* wave of the left atrial pressure pulse.

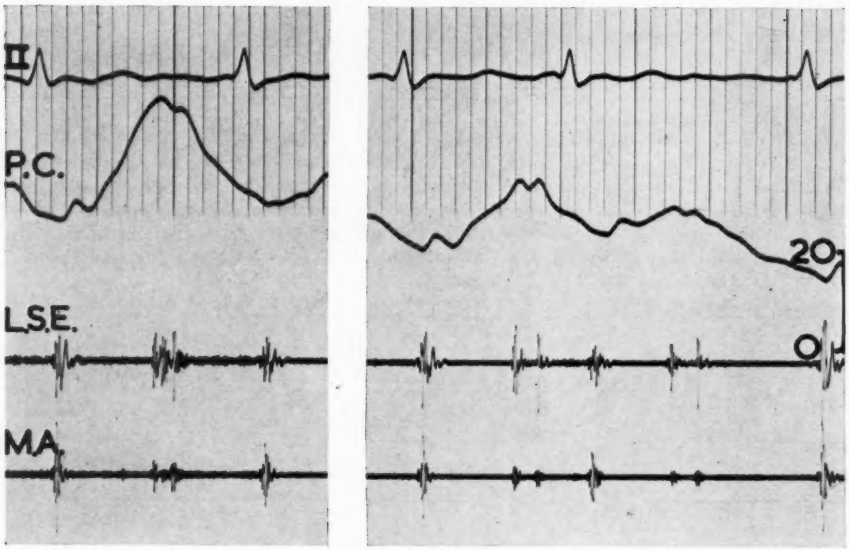

FIG. 2.—Tracings arranged as in Fig. 1. In this patient deep respiration was found to produce a marked swing in the "left atrial" pressure. It can be seen that a high pressure at *v* produces a short A–OS interval and that this interval is prolonged when the pressure falls. (This is the same patient as in Fig. 5.)

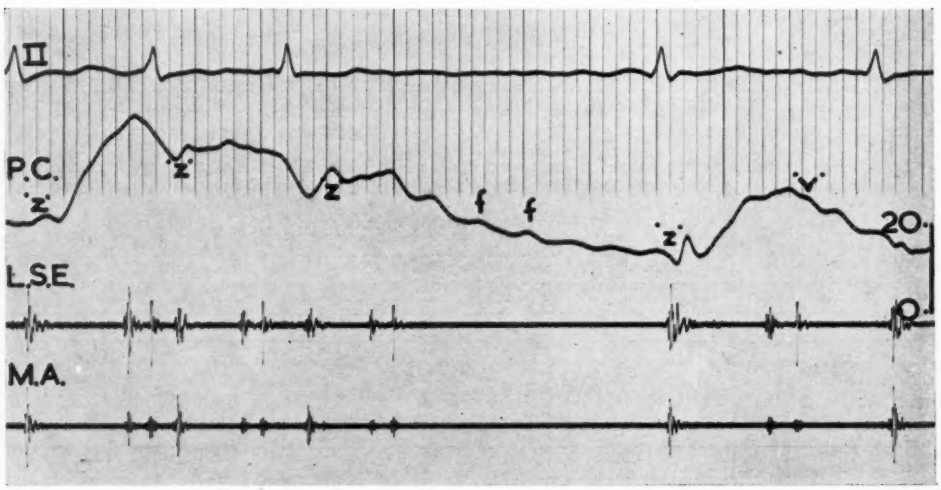

FIG. 3.—Tracings arranged as in Fig. 1. In this patient the effect of a long diastolic pause in shortening the R–M_1 interval and lengthening the A–OS interval is well seen. These changes are clearly related to the synchronous "left atrial" pressures at *z* and *v*. Artefacts at the time of the first heart sound are prominent and there is further distortion of the pressure tracing by fibrillation waves.

In most of the patients a brachial artery tracing was obtained as part of the catheter procedure. A dicrotic notch could be identified in all and was taken as indicating the pressure at the time of aortic valve closure. Lead II of the cardiogram was recorded routinely and measurements of the R–M_1 interval were taken from the peak of the R wave to the initial large vibration of the first heart sound.

High-frequency, logarithmic phonocardiograms (Leatham, 1952) were obtained with microphones placed at the cardiac apex and the fourth left interspace close to the sternum. In all records the mitral first sound, the aortic and pulmonary components of the second sound, and the opening snap were clearly distinguishable. In many of the records the tricuspid first sound could also be identified.

RESULTS

R–M_1 Interval Correlated with the Pressure Level at z. The relationship between the R–M_1 interval and the level of pressure at *z* is shown in Fig. 4. In 300 normal and abnormal subjects with conditions other than mitral stenosis, the R–M_1 interval did not exceed 0·045 sec. In half of our patients with mitral stenosis this interval was within this normal range. Even in the

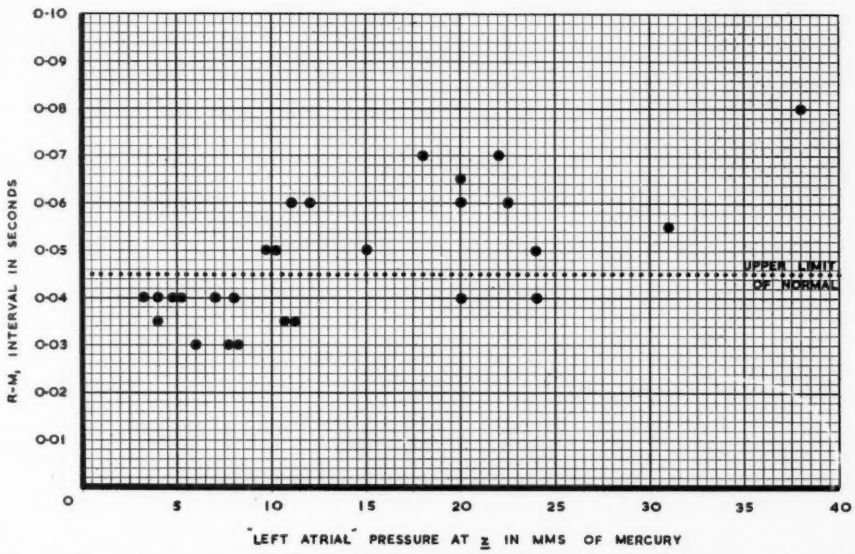

FIG. 4.—The relation between the R–M_1 interval and the simultaneous " left atrial " pressure (at *z*) in 27 patients with mitral valve disease.

remainder, where the R–M_1 interval was outside and often well outside normal limits, the correlation was poor. The results in two patients who showed wide variations in pressures and times have been recorded: in one (Fig. 5) the relation between the R–M_1 interval and the pressure at *z* was rather closer than the results in the whole group of patients (Fig. 4), but in the other there was no correlation at all (Fig. 6). Reasons for these discrepancies will be considered later.

A–OS Interval Correlated with the Pressure Level at v. There was a fair correlation between the A–OS interval and the level of pressure at *v* and this relationship appeared to be linear (Fig. 7). In the two patients already mentioned (Fig. 5 and 6) the correlation was much closer. Returning to the results as a whole (Fig. 7) it seemed probable that the scatter was due to differences in aortic pressure between one patient and another. For example if two patients have the same *v* pressure, the A–OS interval should be longer in the one with the higher aortic pressure. This relationship is illustrated in Fig. 8, where the aortic valve closing pressure has been plotted as a hypothetical value of *v* at which the A–OS interval would be zero. This value for each patient has been joined

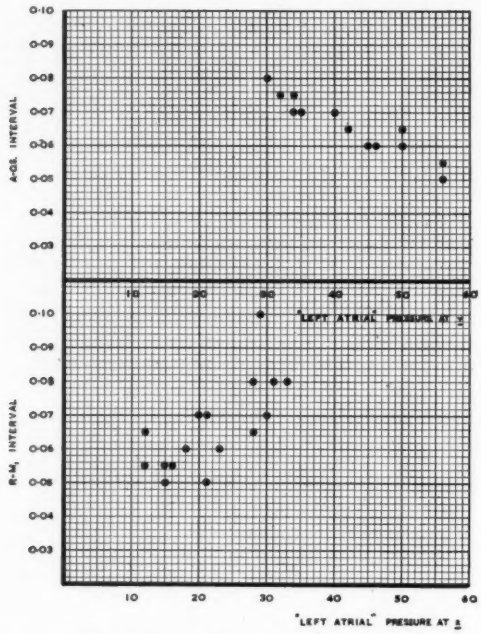

FIG. 5.—In this patient with mitral stenosis and auricular fibrillation, deep respiration produced a wide swing in "left atrial" pressure. There was a good correlation between the varying A–OS interval and the simultaneous pressure (at *v*). Unlike the patient in Fig. 6, the R–M_1 interval did show some variation though the correlation with the simultaneous pressure (at *z*) was only fair.

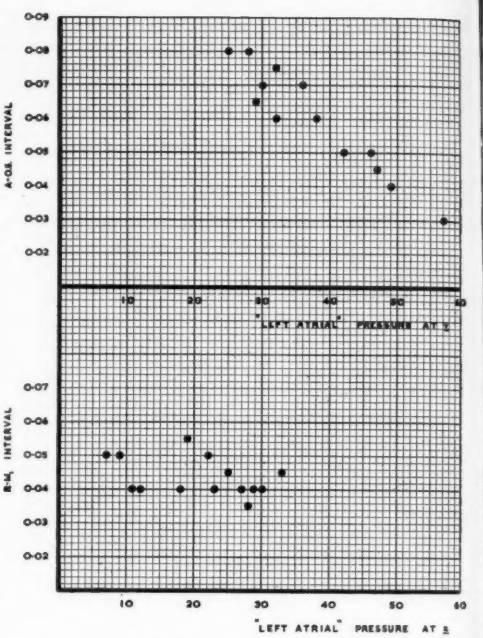

FIG. 6.—In this patient with mitral stenosis, aortic incompetence, and auricular fibrillation, exercise produced a sharp rise in the "left atrial" pressure. The A–OS interval shortened and there was a good correlation between this interval and the simultaneous pressure (at *v*). There was little change in the R–M_1 interval and no correlation between it and the rising "left atrial" pressure (at *z*).

to a second point relating the actual A–OS interval with the measured left atrial pressure at *v*. It is then clear that high aortic pressures do make the opening snap occur later and that low aortic pressures are associated with early opening snaps. The slope of the lines joining the paired points is an expression of the rate of isometric relaxation and in these patients showed little variation.

DISCUSSION

R–M_1 Interval. It is now generally accepted that mitral valve closure produces the first, and tricuspid valve closure the second component of the first heart sound. The time of mitral valve closure as expressed by the R–M_1 interval could be influenced by the following factors: (1) the pressure gradient between the left atrium and left ventricle at the onset of ventricular systole, (2) the rate of rise of ventricular pressure, (3) the electrical-mechanical interval of the left ventricle, and (4) the pliability of the valve.

Other workers on this subject have thought that the height of the left atrial pressure is the chief factor in prolonging the R–M_1 time (Messer *et al.*, 1945; Kelly, 1955). Kelly points out that mitral stenosis is the only condition in which the Q–M_1 interval is prolonged. In mitral incompetence there is no gradient and this interval is normal. Kelly found, however, that only half his patients with mitral stenosis showed an increase of the Q–M_1 interval and that in some with tight mitral stenosis it remained within the normal range. These observations correspond with our experience (Fig. 4). If the R–M_1 interval was prolonged, then the coincident left atrial pressure was always

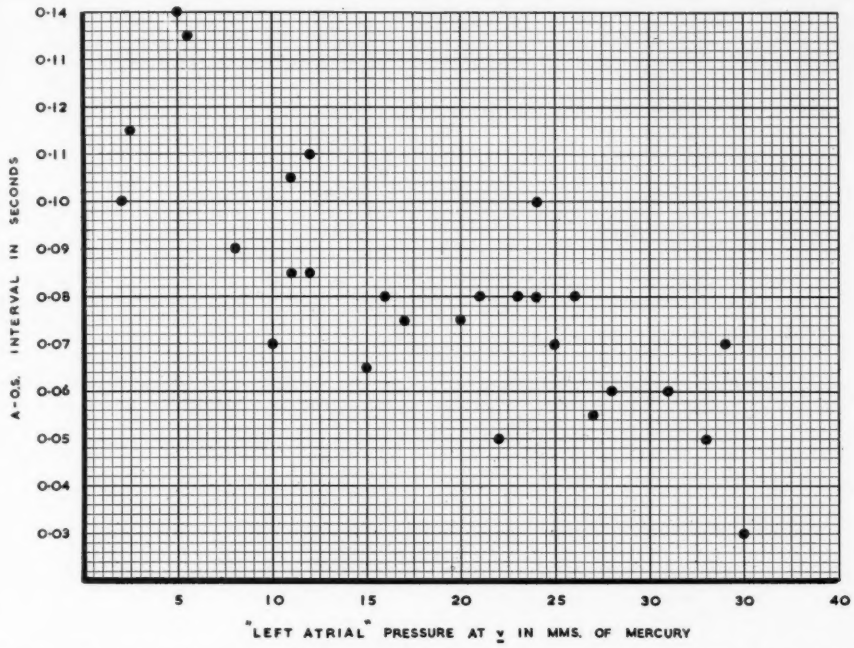

FIG. 7.—The relation between the A–OS interval and the simultaneous " left atrial " pressure (at *v*) in 27 patients with valve disease.

found to be raised. However, the converse does not hold and a rise of pressure may occur with no increase of this interval. The value of this measurement is therefore limited and it cannot be used to derive an index of the degree of mitral valve obstruction.

However, this discrepancy is of considerable interest, and the most satisfactory explanation of it is that the left ventricular pressure must rise more rapidly in some patients than in others. The rate of pressure rise when measured at operation varied between 4 and 14 mm. Hg per 0·01 sec.; this was in patients with mitral stenosis, but details of associated valve lesions were not given (Kelly, 1955). It seems reasonable to suppose that an aortic valve lesion would be the most likely cause of an increased rate of rise of left ventricular pressure, but it would have to be of more than trivial degree. Two outstanding examples of patients with a raised left atrial pressure (*z* levels of 20 and 24 mm. Hg) and normal $R–M_1$ intervals both had important aortic incompetence (Fig. 4). One is the patient whose complete data are given in Fig. 6, and although the left atrial pressure varied widely it showed no correlation with the synchronous $R–M_1$ intervals. In contrast, in Fig. 5 there is a fair correlation between the $R–M_1$ intervals and simultaneous left atrial pressures and this patient had no aortic valve lesion.

Another possible explanation is that, if for any reason there was a rise in left ventricular diastolic pressure, the gradient between left ventricle and atrium would be decreased and this would shorten the $R–M_1$ interval. However, this state of affairs was unlikely to have been present in any of our patients. Another factor that might account for the discrepancy, though very little is known about it, is the electrical-mechanical interval of the left ventricle which has been reported (Kelly, 1955) to vary between 0·02 and 0·06 sec. This range is wide enough for the interval or delay to be a potential cause of substantial differences in the $R–M_1$ time.

Some workers (Wells, 1954; Nichols *et al.*, 1955) have suggested that rigidity and calcification of

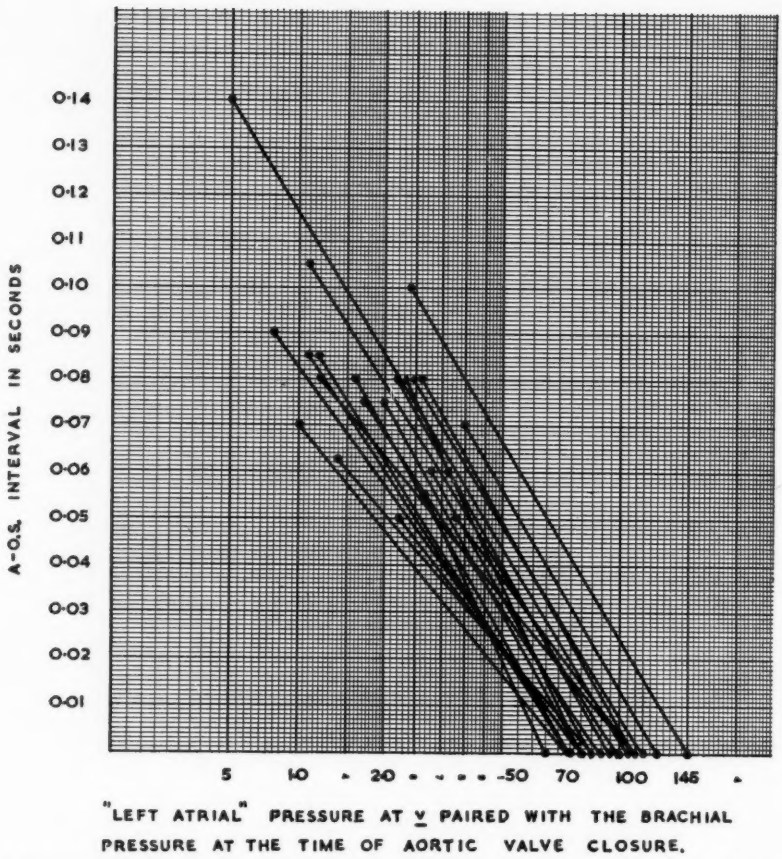

FIG. 8.—In mitral stenosis it is theoretically possible for the A–OS time to be zero; this state of affairs would require the "left atrial" pressure to equal the left ventricular pressure at aortic valve closure.

In each of these patients the aortic valve closing pressure has been taken from the brachial artery tracing and plotted as a hypothetical value of *v*. Each value has been joined to a second point which relates the actual A–OS time with the measured pressure level at *v*. The slope of the paired points is fairly constant and illustrates how the time of occurrence of the opening snap partly depends on the aortic pressure.

the mitral valve might cause delay in closure and lead to a prolonged Q–M_1 time. This seems improbable; most patients with mitral incompetence have rigid valves but an increase of the Q–M_1 interval is not met with in this condition. Further, if such changes delayed mitral valve closure they should also delay mitral valve opening but, as will be seen, there is no evidence of this.

There are, therefore, several factors that might influence the relation between the R–M_1 interval and the coincident left atrial pressure. They limit the value of the phonocardiogram as an indication of this pressure.

A–OS Interval. It would seem probable that the following factors could influence the A–OS interval: (1) the height of pressure in the left atrium, and (2) the height of pressure in the left ventricle at the end of systole (i.e. aortic valve closure pressure).

The importance of the left atrial pressure in determining the time of mitral valve opening is most simply illustrated when there is auricular fibrillation. Margolies and Wolferth (1932) noted that the snap was earlier following a short diastolic period than after one long enough to allow more complete emptying of the left atrium with a corresponding fall in pressure. This mechanism is illustrated in Fig. 3. The timing of the opening snap is accepted as giving evidence of the height of the coincident left atrial pressure and our findings show that this relationship is a linear one. There are, however, two points of practical importance that require emphasis. The first is that the A–OS interval should be correlated with the pressure at *v* and not the mean capillary venous pressure as was done by Bayer *et al.* (1956). It is true that in mitral stenosis, both *v* and *z* frequently approximate to the mean and therefore both *v* and the mean may correlate well with the A–OS interval. But in mitral incompetence where there is a steep *v* wave this will not be so. In our group of 27 patients, there were four who had some incompetence in addition to stenosis and a further two where the incompetence was dominant. In these six, the relation between the left atrial pressure at *v* and the A–OS interval was similar to that in the others with pure mitral stenosis. It follows that when a mixed lesion is present, an early snap is not reliable evidence of a raised mean left atrial pressure.

The second point is that the A–OS interval and the left atrial pressure at *v* are not a direct index of the size of the mitral valve even when there is no incompetence; and this is because of another variable, the cardiac output. With moderately severe mitral stenosis and a large flow, the pressure at *v* will be high and the A–OS interval short. With the same sized valve the findings will be very different with a small flow. This point may also be illustrated at the bedside where the A–OS interval can often be heard to vary with respiration, for in the presence of tight mitral stenosis, the increased pulmonary flow resulting from inspiration raises the left atrial pressure and the snap becomes earlier.

The other factor that is known to influence the timing of the opening snap is the aortic pressure. Bayer *et al.* (1955) were able to lengthen the A–OS interval by raising the systemic pressure with nor-adrenalin, the left atrial pressure remaining unaltered. Our findings confirm the importance of this factor and in Fig. 8 it will be seen that high aortic pressures make the opening snap later and low aortic pressures make it earlier.

Although variations in the rate of rise of left ventricular pressure have been reported there is little information about the rate of fall of pressure. Our results show indirectly that in our patients there was little variation and this factor may be of no importance in determining the time of mitral valve opening. When the systemic pressure has been taken into account, the correlation between the A–OS interval and the simultaneous left atrial pressure is close enough for us to believe that no further factors are involved. There is thus no reason to suppose that changes in the rigidity of the cusps are of any importance in determining the time of occurrence of the opening snap.

Summary

Twenty-seven patients with mitral valve disease were studied by synchronous cardiac catheterization, phonocardiography, and electrocardiography with the object of examining the relationship between intracardiac pressures and the times of occurrence of the first heart sound and opening snap.

The R–M_1 interval (from the onset of the intrinsicoid deflection to the onset of the maximal vibrations of the first heart sound) was within normal limits in half these patients, even though the simultaneous left atrial pressure (at *z*) was sometimes raised. In the remainder the R–M_1 interval was increased but the correlation between interval and pressure was poor. These discrepancies are probably due to differences in the rate of rise of left ventricular pressure, and a rapid pressure rise shortens the R–M_1 interval back towards normal limits. Such a rise could result from associated aortic valve lesions which were found in the discrepant cases. The value of the measurement in predicting the simultaneous left atrial pressure is thus limited; however, it always appeared to be raised when the R–M_1 interval was prolonged.

The time of occurrence of the opening snap, expressed as the A–OS interval (from the onset of the first component of aortic valve closure to the opening snap) showed a fair correlation with the coincident left atrial pressure (at *v*). This relationship, which appeared to be linear, was also dependent on the level of pressure in the left ventricle at the time of aortic valve closure. High aortic pressures make the opening snap later and low aortic pressures make it earlier.

We wish to express our thanks to Dr. Paul Wood for his advice and criticism.

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THE SIZE OF THE LEFT ATRIUM IN CONDITIONS OTHER THAN MITRAL VALVE DISEASE

BY

B. W. COBBS,* J. P. SHILLINGFORD,† AND R. E. STEINER

From the Departments of Medicine and Radiology, Hammersmith Hospital, Postgraduate Medical School of London

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The relatively frequent observation that patients with hypertensive cardiovascular disease had X-ray evidence of left atrial enlargement led us to do a combined radiological and post-mortem study of this chamber, and the purpose of this paper is to show that considerable enlargement of the left atrium may occur in the absence of mitral valve disease.

Historical Note

The association of left atrial enlargement with mitral disease was clearly appreciated in the writings of Corvisart (1806). The displacement of the œsophagus by the enlarged atrium was noted in 1910 by Kovács and Stoerk. In 1920 Kreuzfuchs introduced the use of barium in the œsophagus as a means of outlining cardiac and other intrathoracic structures. Within a few years the technique was securely established as a means of detecting the left atrial enlargement of mitral stenosis (Rigler, 1929). Somewhat similar X-ray abnormalities were soon noted in other conditions by Parkinson (1936) and Rigler (1933). In 1937 Babey summarized these reports and added other examples, which included patients with atrial septal defect, coarctation of the aorta, essential hypertension, aortic valve disease, thyrotoxicosis, and prolonged atrial fibrillation: the majority of his patients had evidence of cardiac failure. A few were examined post-mortem and in some, but not all of his cases the left atrial enlargement was thought to have been confirmed pathologically. Epstein and Schwedel (1938), in a combined radiographic and necropsy study, which included 54 cases of non-valvular heart disease, found evidence of left atrial enlargement by inspection in 25 at necropsy; there was a good correlation of pathological and fluoroscopic data. More recently, Evans (1952) has pointed out that radiological evidence of left atrial enlargement often occurs in constrictive pericarditis. Kjellberg (1955) has noted the left atrial enlargement of ventricular septal defect and persistent ductus arteriosus in children.

None of these observers, however, attempted to confirm the fact of left atrial enlargement by any quantitative method. Stephen Hales in 1733 was probably the first to measure the heart cavities directly: using a standard pressure, he filled the hearts of animals with molten wax, the volume of which was then determined by its displacement of water. Hiffelsheim and Robin in 1864 used the same method to measure the capacity of the human heart chambers: they found the normal left atrium to contain 100–130 c.c. Hochrein in 1927 using water at a pressure of 8 cm. found an average capacity of 140 ml. for the normal left atrium in 30 cases. Friedman in 1951 noted that total heart volumes calculated from their data were significantly higher than those given by modern radiographic estimates, and he concluded that deficiencies in the test conditions had dilated some or all of the heart cavities beyond their usual state in life.

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† Member of the Scientific Staff of the Medical Research Council.

METHODS

Of 163 hearts studied from 6 to 72 hours after death, 53 were controls and 110 included those with rheumatic, hypertensive, coronary, and pulmonary heart disease. In addition to routine examination at the necropsy the heart was removed intact with at least a quarter inch of the pulmonary veins and suspended upright in a lukewarm water bath: the left ventricle and atrium were distended by two rubber condoms attached to glass burettes by stiff rubber sleeves (Fig. 1). The condom in the ventricle was filled with water to close the mitral valve; the atrial condom was then filled to a pressure of 30 cm. of water. Four measurements of the volume of water used to distend the atrium to this pressure were made and usually agreed to within 5 ml.

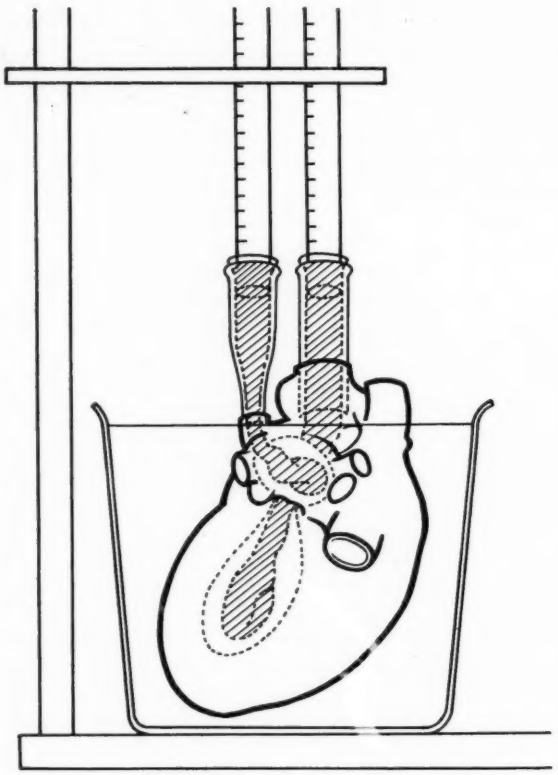

FIG. 1.—The method of measuring left atrial size at autopsy.

Error Limits of Post-mortem Measurements. Measurement of the left atrial size were made at 8, 12, 24 hours and daily after death in six hearts kept moist with normal saline at 40° F. In two an additional measurement was made within 2 hours of death. No significant change of volume was found in the serial measurements from 8 hours after death, although a slight diminution of volume appeared in the first few hours probably due to rigor mortis.

A comparison was made between recorded volumes with and without a rubber condom: the introduction of the latter appeared to reduce slightly the measured volume but could be compensated by an increase in the pressure from 18 to 30 cm. of H_2O. This arbitrary pressure which was adequate to distend the atrium was used throughout and no attempt made to equate it to the left atrial pressure in life.

The left atrial size was assessed radiologically by the standard criteria outlined by Rigler(1929) and Evans (1936). Reliance was placed on the deflection of the barium-filled œsophagus in the oblique and lateral projections and the left atrial outline visible through the heart shadow on the right side; 45 patients were studied within six weeks of death and, independently of the post-mortem measurements results classified as normal, probably enlarged, and enlarged. Ten had mitral heart disease and 35 included hypertensive, aortic, coronary arterial, and pulmonary heart disease.

Results

The size of the atrium in the control group appeared to be related to the total body height and correction was made for this by adjusting all the observations to the mean height by a regression equation. Fig. 2 shows the volumes in the normal male and female group. In the former the size varied from 60 to 115 ml. and in the latter from 60 to 90 ml.

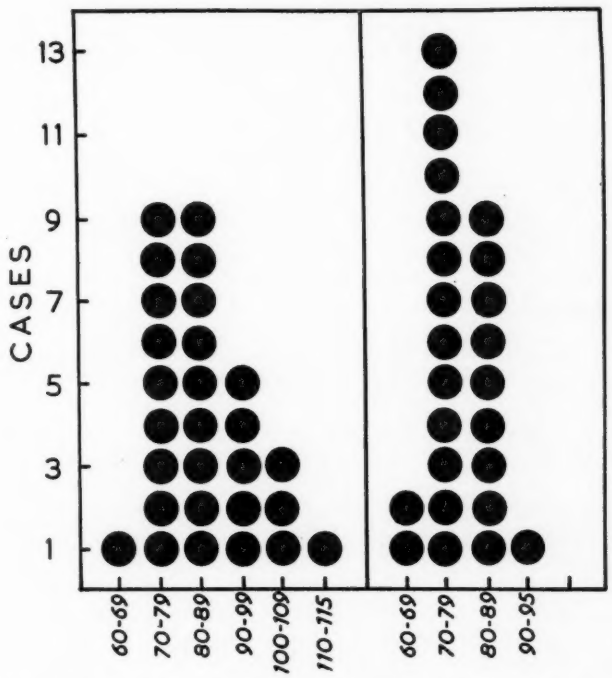

FIG. 2.—The left atrial volume (ml.) in 53 normal hearts at necropsy. Men on the left, women on the right. Each dot represents one case (corrected for height of patient).

Fig. 3 and 4 summarize the left atrial volumes at necropsy in 110 patients with heart disease. The bottom line gives the normal distribution curve. Each of the disease groups has been arbitrarily divided into four subgroups on clinical grounds. (1) Severe disease but no evidence of cardiac failure. (2) Mild disease with no evidence of failure. (3) Cardiac disease with terminal failure of duration of three weeks or more before death. (4) Those in whom cardiac failure was a terminal event, less than three weeks or had occurred in the past for short periods only.

It will be seen that the biggest atria occurred in those with disease of the mitral valve and in one case reached 400 ml. In patients who in life had other forms of heart disease the atrium in many cases was enlarged up to and over 150 ml. which is about twice the average normal size. In many of these heart failure was established but not in all.

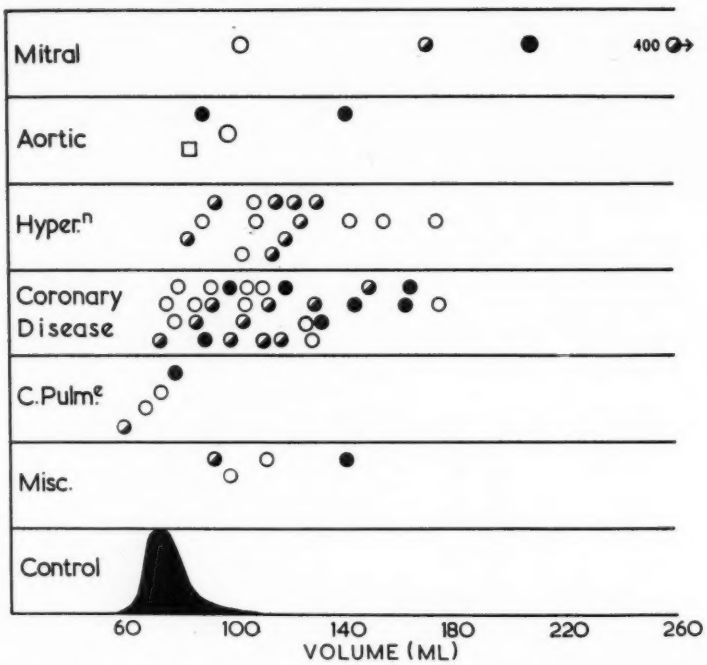

FIG. 3.—The left atrial volumes at necropsy in 59 men dying of various cardiac conditions. Control distribution curve on bottom line. (See Fig. 4 for explanation of symbols.)

Of the 45 patients examined radiologically 22 had a normal atrium confirmed in 21 by necropsy while in 1 the atrium was probably enlarged. In 4 the atrium was probably enlarged radiologically but at autopsy 1 was normal and 3 were enlarged. In the 19 patients with definite radiological left atrial enlargement 1 was normal in size at necropsy, 2 were probably enlarged, and 16 certainly enlarged. The latter included mitral, aortic, hypertensive, and coronary arterial disease (Fig. 5, 6, 7, 8). Left atrial enlargement could usually be diagnosed radiologically when the volume was over 120 ml. as measured at necropsy.

DISCUSSION

The pathological and radiological results show that left atrial enlargement may occur in all types of cardiac disease in which the left side of the heart is involved. Although our pathological studies show that this increase is not as great as with severe mitral disease the volume may be over twice normal in such conditions as hypertensive or ischæmic heart disease. Myocardial failure is often found in this group with enlarged atria but not necessarily so; it is probably reasonable to postulate that the cause of enlargement in hypertensive disease is partly due to left atrial hypertension and, with the development of failure, to generalized cardiac dilatation.

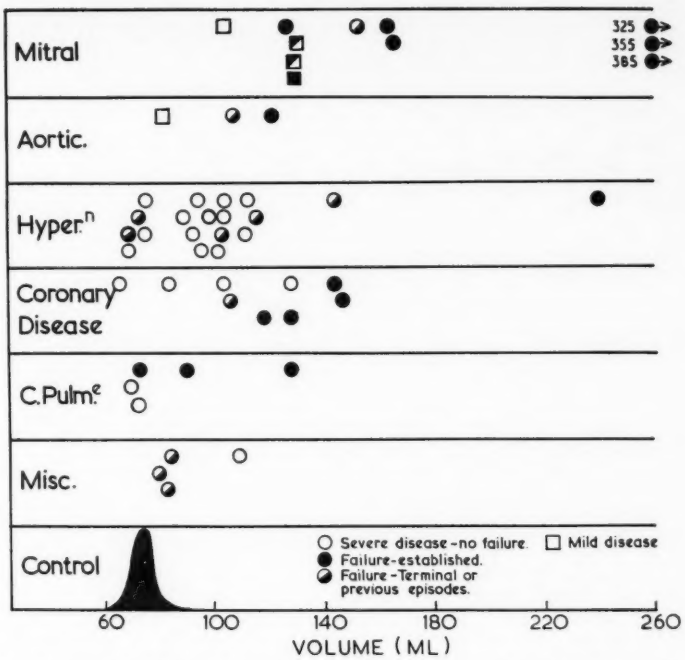

FIG. 4.—The left atrial volumes at necropsy in 51 women dying of various cardiac conditions. (Control distribution curve on bottom line.)

There was good correlation between the radiological findings of atrial enlargement and those found at necropsy.

Unequivocal radiological evidence of enlargement usually occurred when the atrial volume at death measured 120 ml. or more and in view of this it is unlikely that the signs of enlargement are due merely to displacement by the left ventricle.

These results give strong support to the criteria of radiological assessment of left atrial size laid down by Parkinson (1936) and Evans (1936). In assessing the left atrial impression on the œsophagus by an enlarged atrium the oblique projections are the conventional choice, but in our experience and from the results of the present study the left lateral projection is as reliable, which is in agreement with Soloff and Zatuchni (1956).

The double contour sign of an enlarged left atrium along the right cardiac border, although very useful as further indication of left atrial enlargement, is only convincing if the atrium is of such size that the œsophageal impression is quite definite and in itself diagnostic. The results also indicate that very slight left atrial enlargement may not always be demonstrable by radiological methods; nor can one distinguish left atrial enlargement due to mitral valve disease from that seen in other conditions such as hypertension or ischæmic heart disease, except by judgment made from the appearances of other cardiac chambers and the pulmonary vessels.

SUMMARY

To determine the normal size of the left atrium and its size in subjects dying from various types of cardiac disease, 163 hearts have been examined at necropsy.

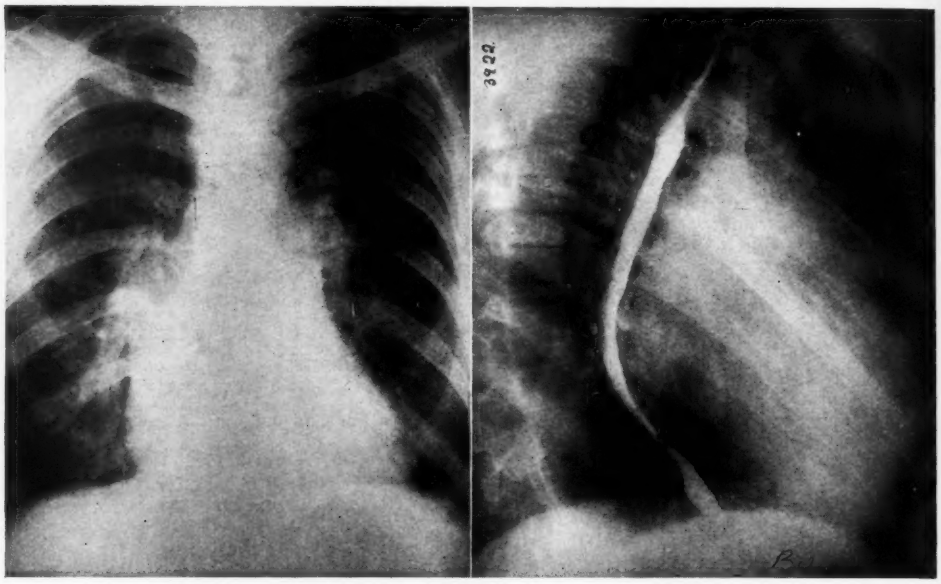

FIG. 5.—Man, aged 36, with mitral stenosis. Postero-anterior and first oblique projections demonstrated considerable left atrial enlargement. Left atrial volume at necropsy: 209 ml.

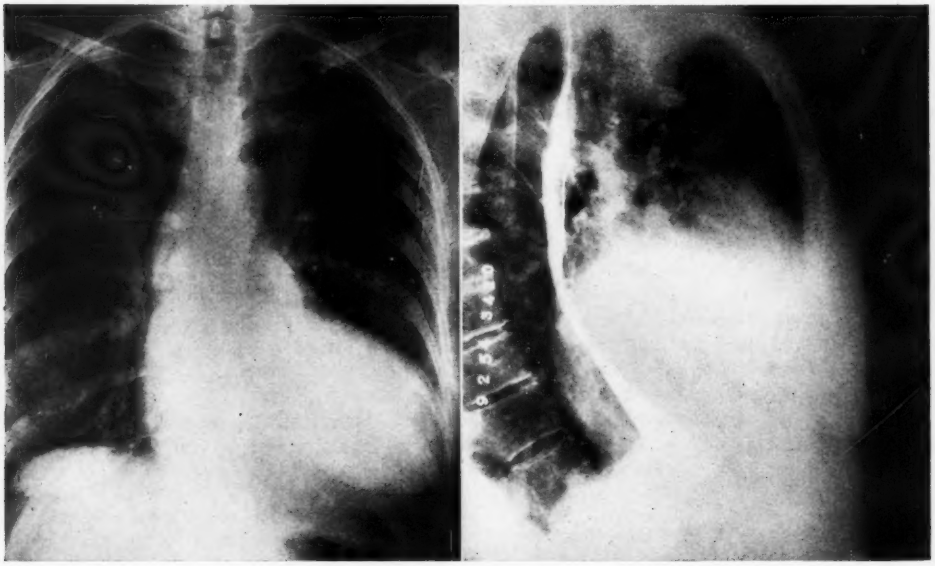

FIG. 6.—Woman, aged 53, with aortic stenosis. Posterior and lateral radiographs demonstrated considerable left ventricular and some left atrial enlargement. Volume of left atrium at necropsy: 124 ml.

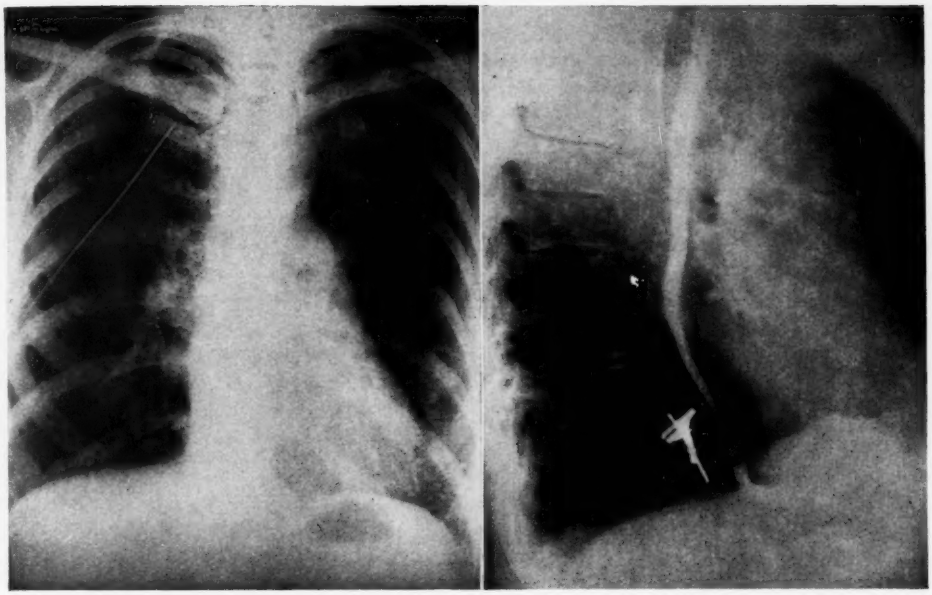

FIG. 7.—Man, aged 44, with essential hypertension. Posterior and lateral radiographs. There is evidence of slight left atrial enlargement. Volume of left atrium at necropsy: 123 ml.

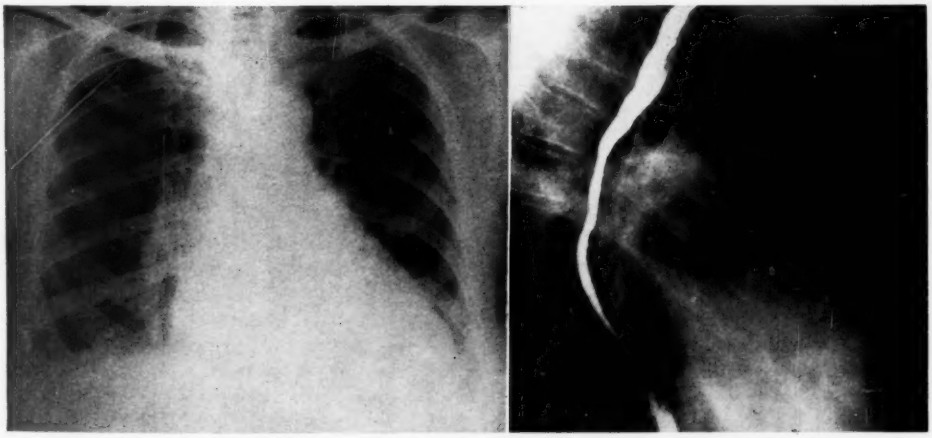

FIG. 8.—Woman, aged 58, with ischæmic heart disease and slight mitral incompetence. Posterior and lateral radiographs demonstrated general cardiac enlargement with definite left atrial enlargement. Atrial volume at necropsy: 145 ml.

These results have been compared with the radiological findings in life.

Although the hearts with mitral valve lesions show the greatest left atria, considerable enlargement may be demonstrated by radiological and post-mortem examinations in those patients who have hypertension, coronary arterial disease, or aortic valve lesions. Although atrial enlargement is present in these in the absence of cardiac failure it is more common when generalized cardiac dilatation has occurred.

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LIPOPROTEINS IN CORONARY ARTERY DISEASE

BY

E. M. M. BESTERMAN

From the Institute of Cardiology

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Lesions of the arterial intima were described in 1804 by Scarpa and cholesterol deposits in the arteries were recognized by Vogel in 1847. The descriptive term atherosclerosis was introduced by Marchand (1904). Subsequently Anitschkow (1913) demonstrated a relationship between these lesions and the serum lipids by the experimental production of atheroma in rabbits fed on cholesterol. The quantitative and qualitative abnormalities of the serum lipoproteins associated with atheroma are not completely understood. The lipoproteins are complex mixtures of lipids linked to the plasma proteins, which have been investigated by three techniques: Cohn fractionation (1950), ultracentrifugal separation (Gofman, 1950; Lewis and Page, 1949), and electrophoresis by both the Tiselius and filter methods. Paper electrophoresis, which is the crudest of these methods but relatively simple and requiring no expensive apparatus, has been used by Nikkila (1953), Swahn (1953), Dangerfield (1955) and others to investigate lipoproteins in diseases with gross lipid abnormalities such as biliary cirrhosis, diabetes, nephrosis, and xanthomata.

The lipoproteins fall into two main groups, β and α, so called by virtue of their proximity to the β and α 1 globulins on electrophoresis. Of the total serum cholesterol, 64 per cent is contained in the β and 24 per cent in the α lipoproteins. Relatively more phospholipid is present in the α lipoprotein; thus the α C/P ratio is lower (0·63) than is the β C/P ratio (1·24) (Nikkila, 1953).

In atheroma, the lipid distribution is altered: an increase of β, and a reduction of the α lipoprotein has been described by Barr (1951), Raynaud (1953), and Nikkila (1953). Oliver and Boyd (1955) have demonstrated corresponding alterations in the absolute cholesterol content of the two lipoproteins. The increased serum C/P ratio in atherosclerosis is another reflection of this redistribution. However, these changes are not sufficiently specific for diagnostic purposes in the individual patient. Page (1954) has correlated the lipoproteins separated by electrophoresis with those found on ultracentrifugation, the Sf 10–20 group which is increased in atheroma (Gofman, 1950) corresponding to the β lipoprotein.

Using paper electrophoresis, Dangerfield noted a pre-β lipoprotein, not commented on previously, in various conditions associated with grossly abnormal lipids, as well as in some cases of coronary artery disease. It seemed possible that this fraction might provide a more specific indication of lipid abnormality in atheroma. It was therefore decided to use Dangerfield's technique in an attempt to evaluate the relationship of this pre-β lipoprotein to atheroma and to coronary artery disease in particular.

Technique. Electrophoresis was carried out by the " draped " or hanging technique of Flynn and de Mayo (1951), using 35 × 5 cm. strips of Whatman No. 3 paper: a thick paper is necessary to accommodate the amount of serum necessary (0·16 ml.) for satisfactory lipoprotein analysis. After application of serum these strips were saturated with barbitone buffer, *p*H 8·6, and a current of 1 mA per strip at 250 V. was applied for 17 hours. For shorter runs of 7 hours, 3 mA per strip was necessary. After drying, the papers were bisected longitudinally; one half was then stained for proteins with Light Green and the other half stained for lipoproteins with Sudan Black B

using Swahn's (1953) technique. The Latner photodensitometer (Latner *et al.*, 1954) was then used to plot graphs from the paper electrophoretograms.

Material and Method. In a study of patients with atheroma it is impossible to provide for comparison a group of normal subjects who are indisputably free from atheroma, and so our control patients undoubtedly include many with some degree of atheroma. In view of such a possible weighting of the control group, any difference emerging on comparison between these and the abnormal subjects may be of greater significance than appears. The 124 control subjects were selected from patients with no clinical, radiological, or electrocardiographic evidence of ischæmic heart disease or atheroma: most were suffering from rheumatic or congenital heart disease and the remainder had no evidence of any heart disease.

The second group of subjects was composed of 200 patients with unequivocal clinical and electrocardiographic evidence of ischæmic heart disease. A third smaller group of 42 patients with aortic atheroma was also studied: they had aortic calcification on fluoroscopy, but no evidence of ischæmic heart disease. The lipoproteins of these subjects were investigated to determine the difference, if any, between gross aortic atheroma and predominant coronary atheroma. For more accurate comparison of the findings between each of these three main groups of patients, further subdivisions were made according to sex and 20-year age groups.

Investigation. Preliminary studies showed that the use of fasting sera had no advantages as the lipoprotein pattern was identical in sera taken before and after a meal. Plasma and serum lipoproteins were identical. Storage of serum at −4° C. for up to three weeks caused no deterioration. Many of the ischæmic patients were in hospital for treatment of acute cardiac infarction, and the transient changes in the lipoprotein pattern observed in these cases will be reported separately. For this reason only those serum samples collected two or more weeks after infarction were used in this study.

Using the Latner densitometer, graphs were derived from the electrophoretograms (Fig. 1 and 2) and the areas of the β, pre-β, and α lipoproteins were determined by planimetry. On these

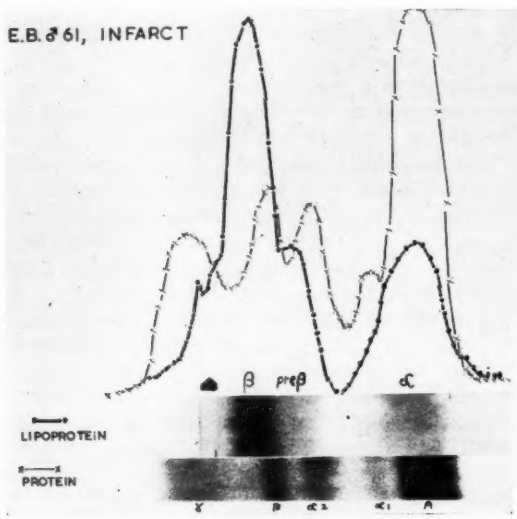

FIG. 1.—Typical electrophoretograms and graphs of plasma proteins and lipoproteins from the serum of a patient with ischæmic heart disease.

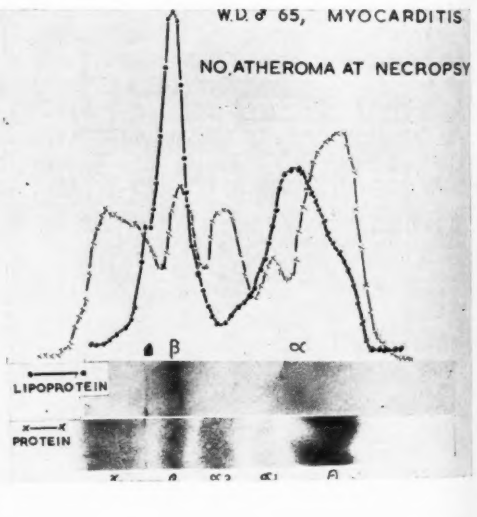

FIG. 2.—Electrophoretograms and graphs of plasma proteins and lipoproteins from the serum of a control subject.

graphs the curve of the pre-β lipid was partially superimposed on that of the β lipoprotein. To obtain the area of each of the lipid bands a perpendicular line was drawn from the nadir of the intersection of the two curves to the boundary between the lipoproteins on the electrophoretogram in position beneath the graph. The resultant pre-β and β areas will be nearly equal to the true area of each curve when extrapolated (Fig. 3). Variations in staining made it impossible to compare

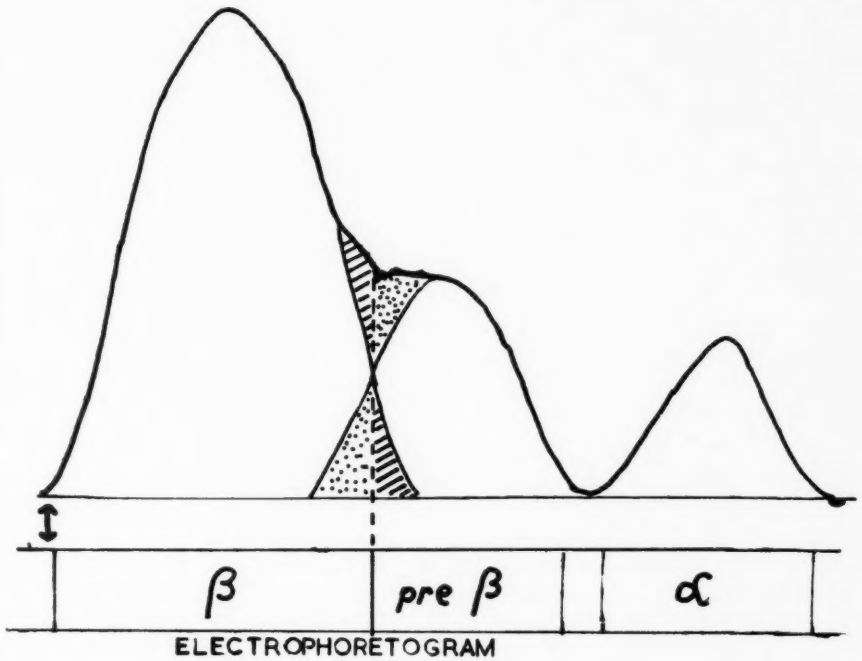

FIG. 3.—Diagram to illustrate the method of determining the areas of the pre-β and β curves when projected as a graph from the electrophoretogram.

the individual lipoproteins in any series of electrophoretograms. Therefore the area of each lipoprotein was expressed as a fraction of the total area of lipoproteins in each electrophoretogram. The differences between the mean findings in the control, and those in the ischæmic and atheromatous groups were then subjected to statistical analysis, and the probability was assessed of obtaining the observed differences by chance alone.

Results. The findings are summarized in Table I and the histograms in Fig. 4 and 5 were derived from this table. There were 46 control subjects under the age of 30 but there were no patients with ischæmic heart disease or atheroma in this age group. The α and β fractions were approximately equal, whereas in the older controls an increasing disparity became apparent. A pre-β lipoprotein was present in some of these younger control subjects.

There was no obvious difference in the β fraction between the three main groups, in either sex, at any age. Individual variations occurred, but the only significant increase of this lipoprotein was seen in a few patients suffering from xanthomatosis and hypercholesterolæmia who were not included in the present study.

A highly significant increase in pre-β lipoprotein distribution was found in both the ischæmic

TABLE I

MEAN VALUES OF EACH LIPOPROTEIN FRACTION IN CONTROL GROUPS COMPARED WITH THOSE IN THE ISCHÆMIC AND ATHEROMATOUS GROUPS

	Age		$\frac{\beta}{\beta+\text{pre-}\beta+\alpha}$	$\frac{\text{pre-}\beta}{\beta+\text{pre-}\beta+\alpha}$	$\frac{\alpha}{\beta+\text{pre-}\beta+\alpha}$	Number of patents
MALES	10–29	Control	0·458±0·012	0·069±0·013	0·463±0·036	27
	30–49	Control	0·517±0·056	0·083±0·016	0·377±0·028	18
		Ischæmic	0·499±0·021	0·219±0·006 $p<0·001$	0·279±0·010 $p<0·001$	46
		Atheroma	0·513±0·022	0·192±0·010 $p<0·001$	0·300±0·036 $p<0·1$	9
	50–69	Control	0·511±0·021	0·093±0·014	0·396±0·027	16
		Ischæmic	0·491±0·013	0·218±0·005 $p<0·001$	0·277±0·007 $p<0·001$	113
		Atheroma	0·472±0·030	0·180±0·015 $p<0·001$	0·313±0·021 $p<0·05$	19
FEMALES	10–29	Control	0·475±0·025	0·068±0·014	0·455±0·029	19
	30–49	Control	0·512±0·016	0·073±0·012	0·416±0·019	30
		Ischæmic	0·480±0·020	0·205±0·012 $p<0·001$	0·315±0·028 $p<0·01$	11
		Atheroma	0·466±0·022	0·143±0·0004 $p<0·001$	0·389±0·019 $p<0·4$	2
	50–69	Control	0·548±0·023	0·116±0·015	0·337±0·019	14
		Ischæmic	0·491±0·025	0·201±0·011 $p<0·001$	0·282±0·022 $p<0·1$	30
		Atheroma	0·507±0·032	0·159±0·024 $p<0·2$	0·333±0·033 $p<0·9$	12

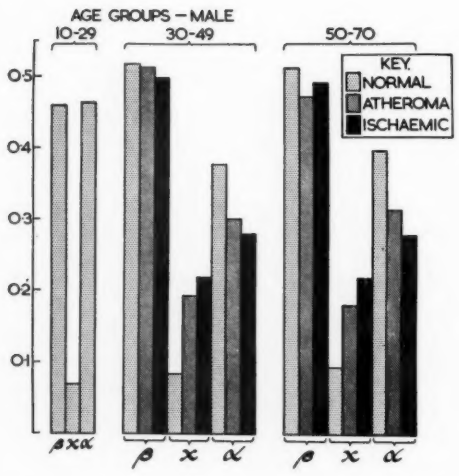

FIG. 4.—Histogram of the lipoprotein fractions in men. x=pre-β lipoprotein. The scale indicates the fraction of the individual lipoprotein as a proportion of the total lipoproteins.

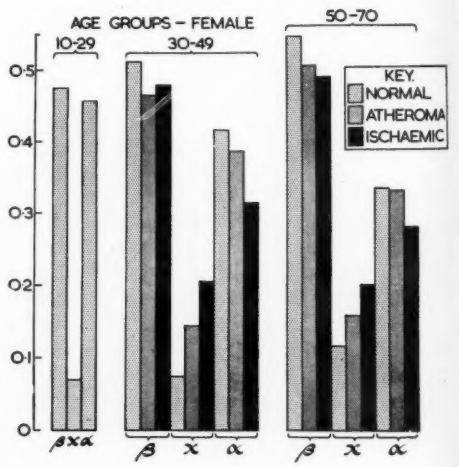

FIG. 5.—Histogram of the lipoprotein fraction in women. x=pre-β lipoprotein. Scale as in Fig. 4.

and atheromatous groups, especially in the former and particularly in men. The pre-β lipid was found in some of the control subjects, and tended to increase slightly with age; it was most noticeable in women over 50.

A pronounced diminution of the α lipoprotein was found in men with ischæmic heart disease, and also to some extent in men with atheroma. The α lipoproteins were diminished slightly in women with ischæmic heart disease, but not at all in women with uncomplicated atheroma. In the control group, women aged 30–49 appeared to have α lipoprotein fractions greater than men; whereas in older subjects this difference between the sexes was reversed.

The lipoprotein pattern in the electrophoretogram of Fig. 1 was typical of that obtained in the ischæmic subjects. A well defined pre-β band was present and the α lipoprotein was diminished. By comparison the normal lipid distribution shown in Fig. 2 contained a large α lipoprotein fraction and no pre-β band. This electrophoretogram was obtained from the serum of a patient who died subsequently from heart failure caused by a cardiopathy of unknown ætiology: no significant coronary atheroma was found at necropsy.

Pre-β Lipoprotein. The pre-β lipoprotein was found repeatedly in the sera of 198 out of the 200 ischæmic subjects (Fig. 6); but was consistently absent in two, in whom further interrogation

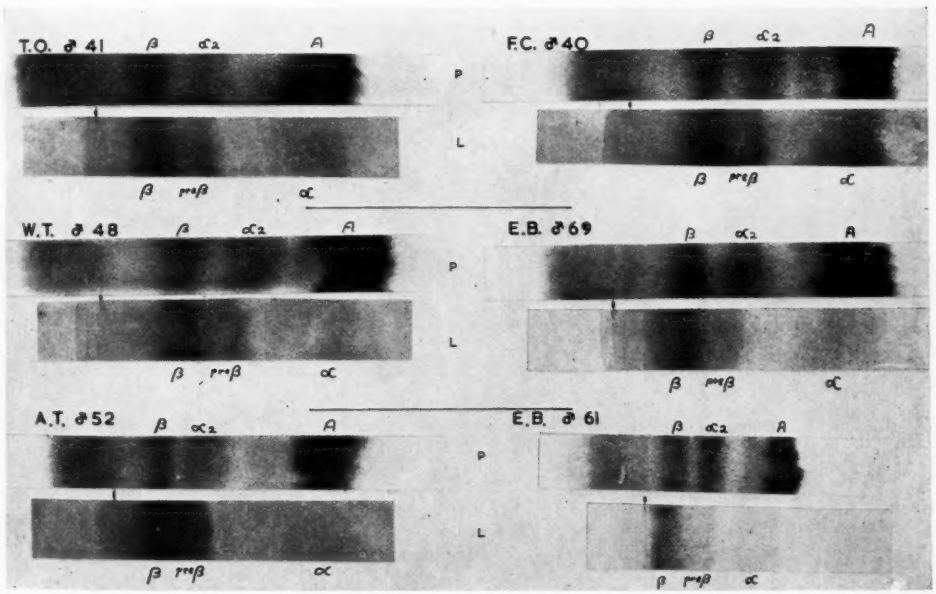

FIG. 6.—Paired electrophoretograms of plasma proteins (P) and lipoproteins (L) to illustrate the pre-β band from six patients with ischæmic heart disease.

and investigation has revealed no explanation for the discrepancy. A pre-β band was found on electrophoresis of the sera of some men and women, aged 20–30, and of some boys under 20 years old, but in no girls. In many of the control sera, the band was either indistinct or absent (Fig. 7).

In order to determine whether the pre-β lipid was distinct in composition from the adjacent β lipoprotein, extracts from each lipoprotein band were analysed by Dr. H. G. Sammons in Professor Frazer's department at Birmingham. The results are shown in Table II: the most obvious

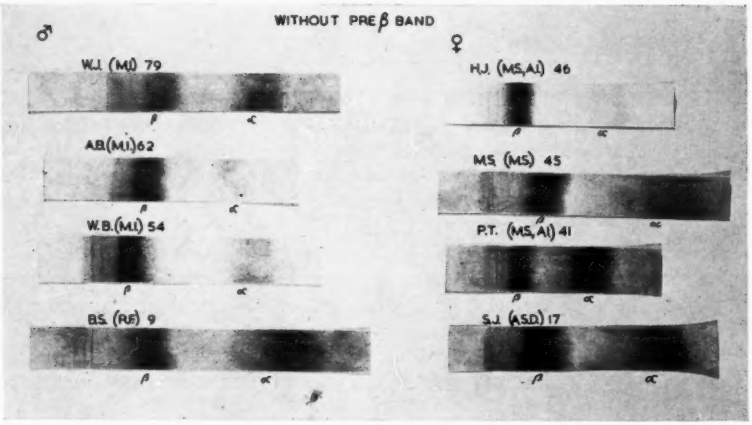

FIG. 7.—Electrophoretograms of the lipoproteins from 8 control subjects. No pre-β lipoprotein present.

TABLE II

ANALYSIS OF EXTRACTIONS OF INDIVIDUAL LIPOPROTEINS AND THE NEUTRAL FAT BAND

	Total lipid	Cholesterol	*p*	Free fatty acid
	mg.	%	%	%
Neutral fat	5·95	25	0·065	19
β	12·30	55	0·037	14
pre-β	7·40	34	0·040	11
α	7·05	20	0·128	16

difference being that the pre-β cholesterol content was 34 per cent whereas that of the beta lipid was 55 per cent. The composition of the pre-β lipoprotein also appeared to be quite distinct from that of the neutral fat band at the point of application of the serum. Dangerfield has already reported that ethanol extraction of the lipoproteins after electrophoresis resulted in extraction of the β, leaving unchanged the pre-β and α fractions.

This pre-β band was found consistently in repeated studies of the same serum, and in serial samples of sera from the same subject. On comparison with the serum proteins the pre-β lipoprotein is not constantly related either to the α 2 or to the β globulin, and appears to lie between the two (Fig. 6). It cannot therefore be termed an α 2 lipoprotein, nor does it result from separation of the β globulin into β 1 and 2 components. This separation of β globulin has not been observed in any routine protein electrophoretograms, nor has it been achieved by alteration of the buffer as suggested by Laurall (1955); nor by use of a borate-barbitone at *p*H 8·6. The pre-β band is also demonstrable on electrophoresis in a horizontal tank, and does not appear to be an artefact due to the " draped " technique. This lipid was equally well seen on both short and long " runs," and does not vary with the degree of migration (Fig. 8). The lack of previous reports on this lipoprotein remain to be explained. Sudan 4 staining showed it as well as Sudan black B. However, the use of 0·06 ml. of serum instead of 0·12 resulted in a poorly defined band (Fig. 9).

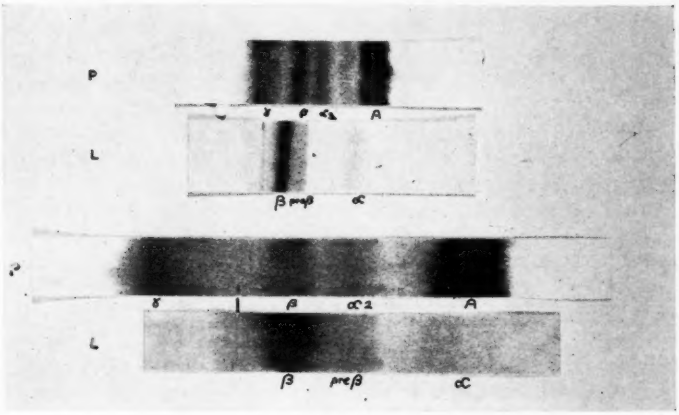

FIG. 8.—Paired electrophoretograms of plasma proteins (P) and lipoproteins (L) to demonstrate distinct pre-β band irrespective of degree of migration.

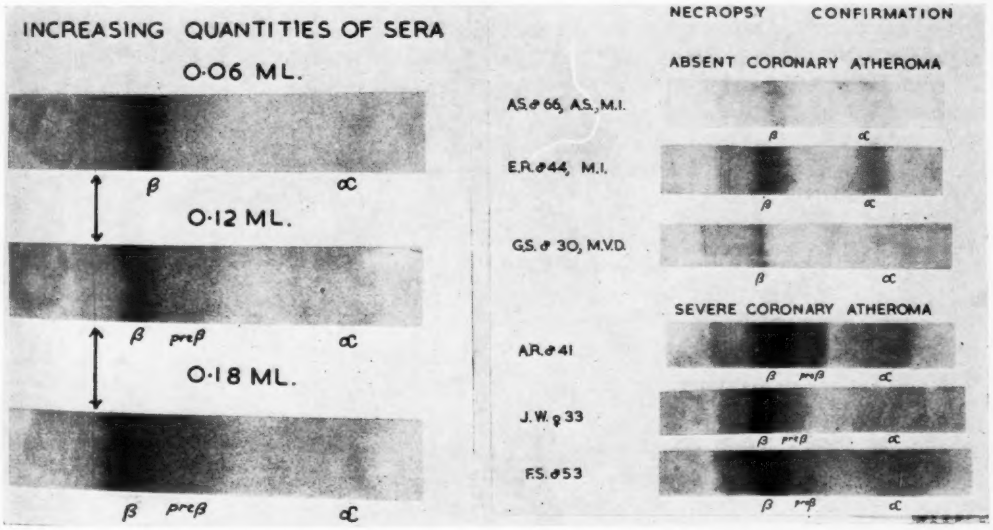

FIG. 9.—Lipoprotein pattern following electrophoresis of increasing quantities of sera. No demonstrable pre-β lipoprotein when 0·06 ml. sera used.

FIG. 10.—Electrophoretograms of the lipoproteins from six patients subsequently examined at necropsy.

Similarly, over zealous washing to obtain a white background after staining with Sudan black resulted in virtual disappearance of the band.

Thus it appears that the pre-β lipoprotein is a distinct entity. It may be present in apparently normal subjects, but is found to a significant extent in 99 per cent of patients with cardiac ischæmia. Seventeen patients in the present series have been examined at necropsy. A significant pre-β lipoprotein was present in each of ten cases with coronary atheroma, but in none of seven without coronary artery disease (Fig. 10).

Cholesterol. The serum cholesterol was estimated by the Myers and Wardell technique, and the results in ischæmic subjects have been compared with those in controls (Table III). Higher

TABLE III

MEAN SERUM CHOLESTEROL VALUES

	MEN				WOMEN			
	No.	10–29	30–49	50–69	No.	10–29	30–49	50–69
Control patients	47	182±18·5 (14)	197±10·4 (18)	164±9·3 (15)	43	148·±11·3 (12)	198±17·9 (19)	206±17 (12)
Ischæmic patients	132	—	160±12·7 (37)	232±4·8 (95)	33	— —	237±20·9 (10)	239±13·3 (23)

mean levels were found in the sera of ischæmic patients, but the variation was considerable and the absolute serum cholesterol was of no diagnostic value in the individual. No relationship was detected between the serum cholesterol and the pre-β lipoprotein. One control subject with a cholesterol of 330 mg. had no pre-β band, whereas several ischæmic patients with a low cholesterol had plentiful pre-β lipoproteins. Gross hypercholesterolæmia with xanthomata was associated with an obvious increase of the β rather than of the pre-β lipoprotein.

THERAPEUTIC EFFECTS

In addition to the lipoprotein pattern in ischæmic heart disease, the effects of various therapeutic agents on each of the three lipid fractions has been investigated. These effects were assessed by comparing the ratio of individual lipid to total lipoprotein before starting treatment, with the ratios found after varying periods of therapy in each patient. The significance of the difference, in either direction, was assessed by a t test.

Fat Restriction. The value of fat restriction is still disputed, but some relationship between fat intake and atheroma undoubtedly exists (Katz, 1955). Twenty patients were treated for 6 to 18 months with a 1500-calorie diet containing 32 g. fat (12 g. animal, 20 g. vegetable fat). Many of these patients were treated initially with a more strict 1000-calorie diet containing 24 g. fat. Apart from this initially severe restriction during treatment in hospital, the therapy was carried out by the patients at home and could not be supervised.

No modification of the lipoprotein pattern was observed after three months' fat restriction, but after six months the pre-β diminished, the α increased, and the β lipoprotein was unchanged. The probabilities of observing these differences by chance were calculated: the values for p were between 0·4 and 0·5 in respect of the pre-β, and between 0·1 and 0·2 for the α fraction. These results suggest a trend toward restoration to normal in the lipoprotein pattern, but the results are not statistically significant. A more strictly supervised short study or else a longer period of observation in these patients would be necessary before any certain biochemical benefit might be shown. The mean blood cholesterol of 270 mg. per 100 ml. showed no significant change after one year. No clinical improvement was found in this group of patients.

Phenyl-ethyl-acetate. This substance was employed as a cholesterol-lowering medium by Cottet (1954). Its suggested method of action involved the blocking of coenzyme A in the liver, thus preventing the formation of active acetate and therefore reducing the synthesis of endogenous cholesterol from active acetate. No toxic reactions were reported.

Eight patients were treated with one gram t.i.d. of phenyl-ethyl-acetamide: toxic effects occurred in all. Generalized erythema occurred in one patient after three days of treatment. Drowsiness and dizziness caused us to stop therapy in a further five patients after three to four weeks and one of these five developed menorrhagia in addition. The drug was withdrawn in the seventh in view of increasingly severe angina, in addition to drowsiness. Recovery from these side effects occurred within four days of stopping treatment. Only one patient tolerated a long course of the drug; an initial four-week period of treatment produced no reaction, and after a month's interval therapy was started again and continued for ten weeks, when it was abandoned because of drowsiness and some erythematous patches.

Since four weeks' treatment was advised by Cottet to ensure a fall in cholesterol, the results in this small series are not strictly comparable with his. However, six courses of three to four weeks' treatment produced no significant change in serum cholesterol (mean 315 before and 350 mg/100 ml. after). In the one ten-week course, the cholesterol levels were 320 before and 310 mg/100 ml. after therapy. Furthermore, weekly lipoprotein studies showed no significant changes in any of these patients when compared with control periods before and after the drug.

Œstrogens. In view of the greater susceptibility of men than women to ischæmic heart disease, œstrogens have been used extensively in experimental studies on atheroma and in the treatment of cardiac ischæmia (Katz, 1953; Oliver, 1954; and Rivin, 1954). High doses have been avoided in the present study, for it was felt that the discomfort of œstrogen side effects was too great a burden to impose on patients already suffering from angina pectoris.

Initially a combination of ethinyl œstradiol and methyl testosterone was used in the hope that the feminizing effects of the œstrogens might be antagonized by the androgen, leaving unhibited the effects on lipoproteins. Since this study was completed Russ (1955) has published evidence that androgens do in fact oppose this action of œstrogens. Our own experience with 13 patients supported this view. Six men and seven women were treated for three months with ethinyl œstradiol 0·06 mg.–0·09 mg. and methyl testosterone mg. 30 daily. No significant change in lipoprotein pattern or in blood cholesterol was observed and this combined hormone therapy was abandoned.

Ethinyl œstradiol alone was then used in small daily doses of 0·05 to 1·0 mg. in 9 women and 18 men. Treatment was abandoned after three months in five of the women owing to menstrual disorders, but was continued in the remaining four. No patient complained of nausea, but mild gynæcomastia developed in five men after nine months' treatment, and was successfully countered by lowering the dose of œstrogen. Two men stopped treatment because they felt that the œstradiol aggravated their angina. No significant clinical improvement was observed in this series of 27 patients; four improved, five deteriorated (one of these died during treatment), and the remainder were symptomatically unchanged.

As only four women continued treatment for six months, no significance can be attached to these results. The results of œstrogen therapy in the 18 men are shown in Table IV. Despite the low dosage of ethinyl œstradiol, a change in lipoprotein pattern was apparent after treatment for one month. No gradual trend was observed in the redistribution of the three lipid fractions in relation to the duration of therapy. However, the lower level of significance attained by the results after 12 and 15 months' treatment is largely due to the smaller number of subjects studied. The individual changes varied (Fig. 11): in some cases an increase of the α with a concomitant decrease of the β fraction occurred, with little change in the pre-β fraction. This effect resulted in a distribution of the α and β lipids comparable to that seen in normal women where the ratio of α to β lipoprotein is higher than in men. In other cases a decrease of the pre-β fraction was as marked as was this feminizing effect. If the pre-β lipoprotein is in any way associated with atheroma, such a change indicated an improvement distinct from that of the solely feminizing redistribution

TABLE IV

CHANGES IN LIPOPROTEIN FRACTIONS OBSERVED IN 18 MEN WITH ISCHÆMIC HEART DISEASE DURING ŒSTROGEN THERAPY

		Mean of difference between start of therapy and					
		After 1/12	After 3/12	After 6/12	After 9/12	After 12/12	After 15/12
$\frac{\beta}{\beta+\text{pre-}\beta+\alpha}$	p	Minus 0·049 <0·02	Minus 0·059 <0·01	Minus 0·062 <0·02	Minus 0·081 <0·001	Minus 0·036 <0·4	Minus 0·048 <0·2
$\frac{\text{pre-}\beta}{\beta+\text{pre-}\beta+\alpha}$	p	Minus 0·038 <0·01	Minus 0·027 <0·02	Miuus 0·052 <0·01	Minus 0·051 <0·01	Minus 0·076 <0·01	Minus 0·064 <0·01
$\frac{\alpha}{\beta+\text{pre-}\beta+\alpha}$	p	Plus 0·087 <0·001	Plus 0·105 <0·001	Plus 0·112 <0·001	Plus 0·137 <0·001	Plus 0·104 <0·01	Plus 0·116 <0·01

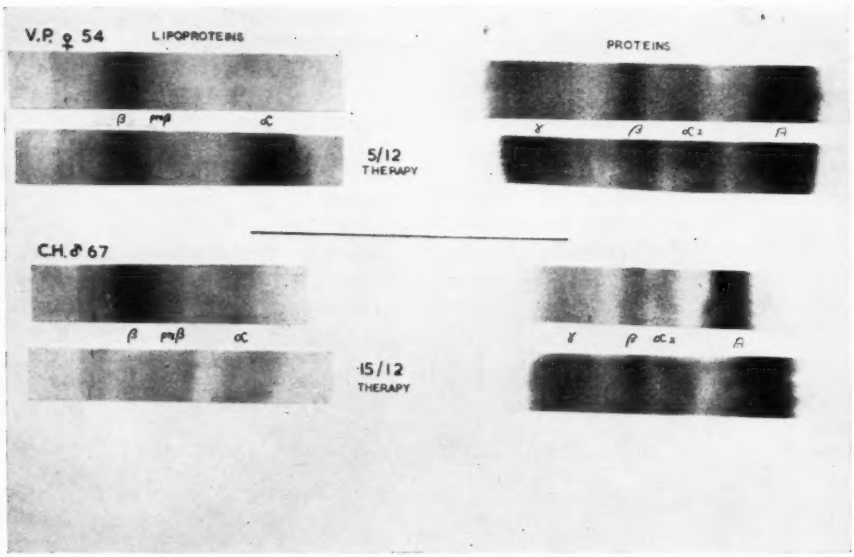

FIG. 11.—Electrophoretograms of lipoproteins and plasma proteins from sera of two patients receiving ethinyl œstradiol. After treatment, the serum of V.P. shows an increase of α and diminution of pre-β lipoproteins. The serum of C.H. shows a large reduction in β lipid, some increase of α and no change in pre-β lipoprotein.

of α and β lipid fractions. The overall results confirmed those of previous workers with regard to the rise of the α and diminution of the β lipids (Robinson, 1955). In addition a decrease of the pre-β lipoprotein occurred. Serum cholesterol values showed a rise from the mean pretreatment level of 228 mg/100 ml. Increases of 7, 11, and 19 per cent were found after treatment for three, six, and twelve months respectively.

In order to determine the effects of massive doses of œstrogens I was supplied, by courtesy of the Institute of Urology, with sera from 21 patients who had received intensive œstrogen therapy for carcinoma of the prostate for 6–24 months: the clinical status of these patients was otherwise unknown to me. The lipoprotein fractions of these patients were compared with those found in men of the same age included in the preliminary study as control, atheromatous, and ischæmic groups (Table V). In the œstrogen treated patients the quantity of α approximated to that of the

TABLE V

COMPARISON OF LIPOPROTEIN FRACTIONS IN VARIOUS GROUPS

	$\frac{\beta}{\beta+\text{pre-}\beta+\alpha}$	$\frac{\text{pre-}\beta}{\beta+\text{pre-}\beta+\alpha}$	$\frac{\alpha}{\beta+\text{pre-}\beta+\alpha}$	Number
Controls *	0·511±0·021	0·093±0·014	0·396±0·027	16
Atheroma*	0·472±0·03	0·180±0·015	0·313±0·021	19
Ischæmia *	0·491±0·013	0·218±0·005	0·277±0·0067	113
Œstrogen therapy	0·471±0·019	0·131±0·017	0·415±0·021	21

* These figures are taken from Table I for men aged 50–69 years.

β lipid in contrast to the excess of β in relation to α lipoprotein found in the other three groups. In the whole of this study, a similar approximation of α and β fractions occurred only in the controls of both sexes under 30 years and in the women of 30–49.

In these œstrogen treated patients with prostatic carcinoma the lipoprotein pattern included a pre-β lipid in many cases. The mean value of this fraction was greater than that found in the control men of the same age, yet less than that of the atheromatous or ischæmic groups. The presence of this abnormal pre-β fraction suggests that even massive œstrogen therapy cannot induce a complete reversion to normal of the lipoprotein pattern. Further conclusions cannot be made from these patients' sera in the absence of a full cardiological assessment and of lipoprotein studies before therapy.

Oral Heparin. The effects of systemic heparin on the lipoproteins have also been studied and will be published separately. Heparin therapy is not yet practical for long-term use outside hospital. However, Laborit (1954) and Scardigli (1955) claimed to have produced a heparin-like action on lipoproteins using a heparin-lipocaic tablet for sublingual administration. A similar sublingual tablet of heparin (without lipocaic) was prepared by Boots, containing 20,000 u. heparin. Seven patients received one to three tablets on 19 occasions; blood samples taken before, 1, 4, and 12 hours after treatment showed no change in lipoprotein pattern. Thus we were unable to confirm the sublingual absorption of heparin. The same patients had previously received 100 mg. heparin intravenously and the lipoprotein pattern was significantly altered in all. This change occurred within three minutes of injection and persisted for 12–18 hours.

DISCUSSION

This study has confirmed the existence of distinct pre-β lipoprotein, first described by Dangerfield (1955). This lipid is insoluble in ethanol and its chemical composition is distinct from that of the adjacent β lipoprotein and of the neutral fat "trail." A similar lipid appears to be present in electrophoretograms published by Rosenberg (1952), Ackmerman (1954), and Jencks (1956), but no previous authors have commented upon it. This oversight may be due to differences in staining techniques and quantities of serum employed. An α 2 lipoprotein has been described by several authorities (Lewis and Page, 1952, 1953; Swahn, 1952; and Nikkila, 1953). The pre-β lipoprotein, as its name indicates, is related to neither β nor α 2 globulin, but lies between the two. The α 2 lipoprotein described by Kunkel (1956) may correspond to the pre-β lipid. However we have not found a postprandial increase of the fraction as he observed.

The present investigation suggests that this pre-β lipid is found mainly in the serum of patients with atheroma. The association is not absolute as no pre-β lipid was found in the sera of two of the 200 patients with ischæmic heart disease. Furthermore a well defined pre-β lipoprotein was found in some young healthy men. The latter finding may be explained by postulating the presence of abnormal circulating lipids, even at a young age. Thus the presence of a pre-β lipoprotein does not provide unequivocal proof of atheroma, but is highly suggestive. This association was further confirmed by comparison of the findings in 17 necropsies with the ante-mortem lipoprotein patterns.

Unfortunately it has proved impossible so far to arrange for ultra-centrifugal analyses of this lipoprotein. According to Page (1954), the β 1 and α 2 lipoproteins correspond to the Sf 1–8 fraction—one that Gofman believes to be little altered in atherosclerosis. Kunkel (1956) has also shown that the Sf$<$12 particles migrate as an α 2 lipoprotein on electrophoresis, a fraction possibly corresponding to the pre-β lipid. It has been suggested by Nikkila (1953) that the smallest lipid particles would be those most probably deposited in the intima. Therefore if a block occurred in the intimal fat metabolism or transport mechanism in atheroma, an increase of the smallest particles would be expected to occur in the serum. This theoretical concept gains some support from a necropsy controlled series of lipoprotein studies published by Paterson (1955). In those patients with atheroma Paterson found a significant increase in the Sf 0–12 fraction alone.

The serum cholesterol level has little relation to the pre-β lipoprotein; cases of hypercholesterolæmia had an increased β lipid fraction. The serum cholesterol level in individual patients provided no significant index of atheroma, although the mean cholesterol value was higher in the ischæmic group than in the control group of subjects.

The pre-β lipoprotein has also been investigated in several series of patients undergoing various therapeutic trials. In these serial studies this lipid has been altered by œstrogen alone, but has never been abolished. The persistence of the pre-β lipoprotein is of particular interest in some patients in whom the α/β ratio reverted to normal. The fourth electrophoretogram (A.R.) in Fig. 10 was obtained from one of these patients: a significant pre-β lipid was present. This 41-year-old man subsequently died, during hormone therapy, and gross generalized coronary atheroma was found at necropsy. Similarly the pre-β lipid was found in some patients receiving prolonged intensive œstrogen therapy for prostatic carcinoma. Therefore it is suggested that this lipoprotein may prove of value in the biochemical study of patients receiving various anti-atherogenic drugs.

In atheroma the α/β lipid ratio is reputedly altered by increase of β and diminution of α lipoprotein. However, this change may have been exaggerated by inclusion of pre-β lipid when measuring the β fraction. From the present study the altered ratios would appear to be due chiefly to reduction of the α fraction and presence of excess pre-β lipid, rather than to any significant increase of β lipoprotein. Thus the pre-β lipoprotein adds a further, and perhaps more specific indication of the presence of atheroma. No one biochemical technique can yet provide an unequivocal answer to the clinician's demand for information regarding the severity of atheroma in a patient. However, the simplicity of paper electrophoresis commends itself, notably in comparison with the technique of ultracentrifugation.

Summary

The pre-β lipoprotein has been shown to have a distinct chemical composition. A significant pre-β lipid has been found in 99 per cent of 200 patients with ischæmic heart disease. This lipoprotein was also found in 42 patients with dominant aortic atheroma and occurred to a lesser extent in some of the 124 control subjects. Statistical comparison between the lipoprotein fractions in the sera of ischæmic and control subjects showed a consistently significant difference ($p<0{\cdot}001$) in the pre-β lipid alone. It is suggested that the presence of a significant pre-β lipoprotein provides a more specific indication of atheroma than does the α/β ratio.

The lipoprotein patterns were studied in different series of patients during treatment by fat

restriction, phenyl-ethyl-acetate, methyl testosterone combined with ethinyl œstradiol, ethinyl œstradiol alone, and by sublingual heparin. Of these only ethinyl œstradiol therapy effected a significant redistribution of lipoprotein. No clinical improvement was observed in any of these series of patients.

I am most grateful to Dr. W. Dangerfield for instructing me in the technique of electrophoresis. Dr. Paul Wood has provided me with invaluable advice and encouragement and I am grateful to him and to the other physicians of the National Heart Hospital for their kind co-operation. I am indebted to Professor A. C. Frazer and to Dr. M. G. Sammons for undertaking the chemical analysis of the lipoproteins. Dr. P. Armitage of the M. R. C. Statistical Research Unit kindly assisted me in the statistical analysis. Beryl Hall provided invaluable technical assistance. The histograms were made presentable by Audrey Besterman.

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A WHOLE BLOOD OXIMETER

BY

I. C. RODDIE,* J. T. SHEPHERD AND R. F. WHELAN

From the Department of Physiology, The Queen's University of Belfast

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During cardiac catheterization it is an advantage to have an immediate indication of the oxygen content of blood samples withdrawn from the heart and great vessels while the catheter is still *in situ*. This is especially important in the more complex congenital defects as the procedure can then be modified if necessary in the light of the blood oxygen estimations.

The present paper describes a whole blood cuvette oximeter that fulfils these requirements and employs a standard portable colorimeter.

METHODS

The Colorimeter. An EEL portable colorimeter is used (Evan's Electro-selenium Ltd.). The only modification is that the 2-volt light source is replaced by a 12-volt car bulb powered by a lead accumulator or a constant voltage transformer. The light from this bulb is focused on the cuvette by a convex lens.

The Cuvette. This is made of pyrex glass and consists of a flat chamber with inlet and outlet tubes of about 1 mm. internal diameter (Fig. 1). The depth of the chamber is about 0·2 mm. and 0·2 ml. blood is sufficient to fill it and 0·4 ml. both the chamber and inlet tubing. The cuvette is mounted with plasticene in a cylindrical brass holder made to the same external dimensions as the standard tubes supplied with the EEL colorimeter. The cuvette is filled through the tube that enters at the bottom since in this way air bubbles are most easily expelled. As the cuvette is not removed from the instrument, the optical properties are constant and it is not necessary that the walls of the cuvette be absolutely flat.

Technique. No filter is employed to reduce the band width of the incident light. An opaque glass filter is constructed so that when it is placed in the light path in front of the cuvette filled with saline the optical density is similar to that of the cuvette filled with blood. This filter provides a reference optical density in setting up the instrument and the optical densities of all blood samples are determined in relation to this reference filter. The optical density of fully reduced and fully oxygenated blood is determined at the commencement of the procedure. For the oxygenated sample, a few ml. of blood are rotated in a small corked flask. To reduce the blood fully 0·1 ml. of freshly prepared saturated sodium hydrosulphite solution is added to 5 ml. of blood. The test samples are then run through as required and their optical densities determined. The percentage saturation of a given sample is derived from the ratio $D_R - D_T / D_R - D_O$, where D_R, D_O and D_T represent the optical densities of the fully

FIG. 1.—The cuvette (see text).

* Walter Dixon Memorial Scholar (British Medical Association).

reduced, the fully oxygenated, and the test samples respectively. The value so obtained is converted into percentage saturation using the calibration curve shown in Fig. 2.

The oxygen capacity of the blood is derived from the difference in optical density between the fully reduced and the fully oxygenated samples, this value being converted into oxygen capacity in volumes per cent by the use of the calibration curve shown in Fig. 3. The oxygen content is derived from the oxygen saturation and capacity.

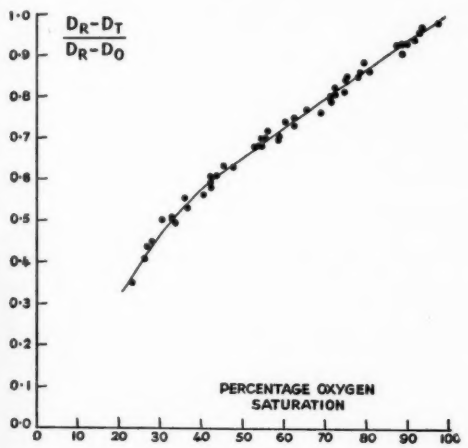

FIG. 2.—Calibration curve for the determination of blood oxygen saturation. D_R, D_T, and D_O represent the optical densities of the reduced, test, and oxygenated blood samples respectively.

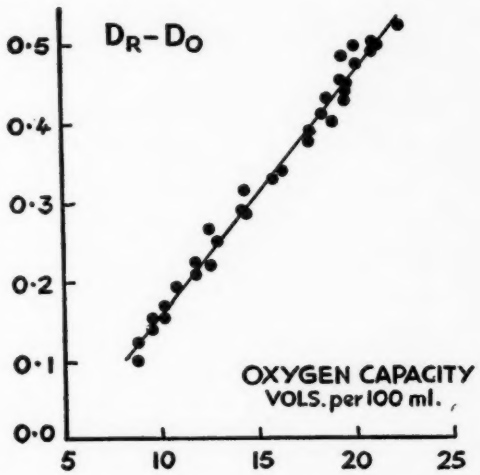

FIG. 3.—Calibration curve for the determination of blood oxygen capacity. D_R and D_O represent the optical densities of the reduced and oxygenated blood samples respectively.

RESULTS

The calibration curve from which oxygen saturation is deduced from optical density measurements was constructed by obtaining the oxygen saturation of 50 consecutive blood samples by a spectrophotometric technique employing hæmolysed blood (Roddie *et al.*, 1957) and plotting these values against the optical density measurements. The standard deviation of the individual points from the curve drawn by inspection was 1·74 per cent saturation and this curve (Fig. 2) is used in the subsequent transfer of optical density ratio into percentage oxygen saturation.

The oxygen capacities of 32 blood samples were determined in a similar manner and plotted against the difference in optical densities between reduced and oxygenated samples. The linear regression of the points so obtained was determined and the standard deviation from the regression line was 0·79 volumes per 100 ml.

DISCUSSION

The value of a whole blood cuvette oximeter for cardiac catheterization is undoubted. Wood (1950) has devised a cuvette oximeter with a high relative accuracy, but there is no such instrument commercially available in this country, though Handforth (1952) has devised a cuvette using a modification of the EEL colorimeter which is suitable for whole blood. The present method is based on a spectrophotometer method using hæmolysed blood (Roddie *et al.*, 1957), but as with all photometric methods, calibration curves must be obtained for each cuvette and instrument used.

From the optical point of view whole blood is an unsatisfactory fluid compared with hæmolysed blood. After the whole blood fills the cuvette the readings do not remain stationary due to changes in orientation and sedimentation of the red blood cells. All the readings must therefore be taken at a standard time after filling the cell. In the technique described in the present paper, the readings were taken immediately after the cell was filled.

Summary

A simple colorimetric method is described for the rapid estimation of percentage oxygen saturation, content, and capacity of small samples of whole blood. The method employs a small glass cuvette in a slightly modified standard colorimeter which enables 1-ml. blood samples to be injected into the cuvette in rapid succession without removal of the cuvette from the instrument.

Calibration curves for percentage oxygen saturation and capacity have been constructed by comparison of the optical density measurements with the values of percentage saturation and capacity obtained by a spectrophotometric technique using hæmolysed blood.

In 50 consecutive blood samples with saturations ranging from 23 to 98 per cent the standard deviation of the differences between values obtained by the two methods was 1·7 per cent. In 32 consecutive blood samples with oxygen capacities ranging from 8·8 to 22 ml. per 100 ml. the standard deviation of the differences between values obtained by the two methods was 0·79 ml. per 100 ml.

We wish to thank Mr. M. L. Speet, Dept. of Physics, The Queen's University of Belfast, who made the cuvettes.

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THE MECHANISM OF THE PULSUS BISFERIENS

BY

PETER R. FLEMING

From the Cardiac Department, Guy's Hospital

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The earliest reference in print to the pulsus bisferiens* is in a Latin edition of Galen's *De Pulsibus*, published in Paris in 1532. From this, it is clear that debate concerning the nature and significance of this type of pulse dates from the first and second centuries A.D. Galen was insistent that, when two separate impulses are felt in the pulse, it cannot be assumed that two separate pulse waves are present. He stated that the pulsus bisferiens (as distinct from the dicrotic pulse) is characterized by *quies media ictus*—a central pause in the stroke.

Although clinical observations on the form of the pulse can be found throughout medical literature, it was not until the invention of the sphygmograph by Marey (1860) that more precise information concerning abnormalities in wave-form became available. Mahomed (1872) who used a modification of Marey's instrument, was the first to use the terms *percussion wave* and *tidal wave*. These terms are now used to denote the twin peaks of the pulsus bisferiens; the anacrotic pulse is characterized by a small percussion wave followed by an unusually tall and broad tidal wave. Broadbent and Broadbent (1900) were among the first to discuss the pulsus bisferiens in aortic valve disease and mentioned the theory of its causation put forward by d'Espine, who suggested that left ventricular contraction occurred in two phases, producing distinct percussion and tidal waves. Bramwell (1937) was not satisfied with d'Espine's explanation and suggested that the tidal wave represented the summation of outgoing and reflected waves. The slowness of left ventricular ejection in aortic stenosis caused the outgoing wave to be well maintained when the reflected wave returned, the resultant summated tidal wave being very large.

Bramwell's explanation of the genesis of the abnormal pulse forms in aortic valve disease has been quoted widely. An alternative explanation, offered by Katz *et al.* (1927), has received less attention. They studied the pressure pulses in the left ventricle and aorta in experimental aortic stenosis in dogs and described a sharp negative deflection occurring on the upstroke of the aortic pressure pulse. This they believed to be due to the suction effect of the high-velocity stream of blood (Venturi effect) and regarded it as the analogue of the anacrotic notch in the peripheral pulse.

The introduction of surgical procedures for the relief of aortic stenosis has provided an opportunity of recording pressure pulses in the aorta and left ventricle in cases of aortic stenosis at operation. It is proposed in this paper to study such records in an attempt to elucidate further the mechanism and significance of the abnormal pulse in aortic stenosis—particularly the pulsus bisferiens. None of the previous theories has explained satisfactorily why the pulse associated with pure or dominant aortic stenosis is characterized by a notch on the upstroke and a large tidal wave, whereas if significant aortic regurgitation is superadded, the pulsus bisferiens with equal, and well defined, percussion and tidal waves is found.

* The derivation of "bisferiens" is from bis-ferio (= beat twice) and not, as is often thought, from bis-fero (= bear twice).

Material and Methods

We have studied 36 cases of aortic stenosis. In some, there was also aortic regurgitation, but in none was it the dominant lesion. Pressure pulses from the left ventricle and aorta were recorded before and after aortic valvotomy; in 29 cases the pressure pulses were recorded simultaneously. Pressures were recorded with 21-gauge needles connected by one metre of hardened plastic tubing to Southern Instruments Minirack electromanometers with a Brush direct-writing recorder.

In cases in which the pressures were recorded simultaneously, the aortic and left ventricular pressure pulses have been redrawn to the same scale and superimposed (Fig. 1 and 2). The gradient across the valve has been measured at intervals throughout systolic ejection and from these

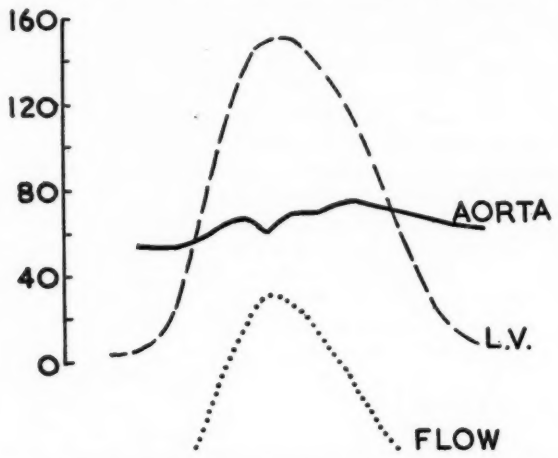

Fig. 1.—Superimposed left ventricular and aortic pressure pulses with flow curve derived from these from a case of aortic stenosis. The apex of the flow curve is synchronous with the aortic anacrotic notch.

measurements a curve representing the changing gradient has been plotted (Fig. 1—lowest curve). The possible error introduced by the measurement of a very high gradient at the nadir of the anacrotic notch was considered and, in practice, measurements were not made at this point. In any case, left ventricular pressure was always so much higher than aortic that quite considerable variations in the form of the aortic pressure pulse had little effect on the form of the gradient curve: the apex of the gradient curve nearly always coincided with the peak of the left ventricular pressure pulse.

The flow through a fixed orifice is directly related to the pressure gradient across the orifice. The gradient curve has, therefore, been used as an approximation to the curve of changing flow through the aortic orifice.

Results

In 28 of the 36 cases a more or less well-defined notch was present on the upstroke of the aortic pressure pulse; this was sometimes associated with high-frequency vibrations of the type recorded by Katz *et al.* (1927) (Fig. 3). The upstroke time of the aortic pressure pulse was always prolonged and the aortic systolic peak delayed relative to the left ventricular peak.

After a successful valvotomy (Fig. 4), apart from the fall in systolic pressure gradient across the valve, the anacrotic notch was often situated higher on the upstroke, nearer the aortic systolic peak. As it moved higher, it was usually less well-defined and sometimes could no longer be identified.

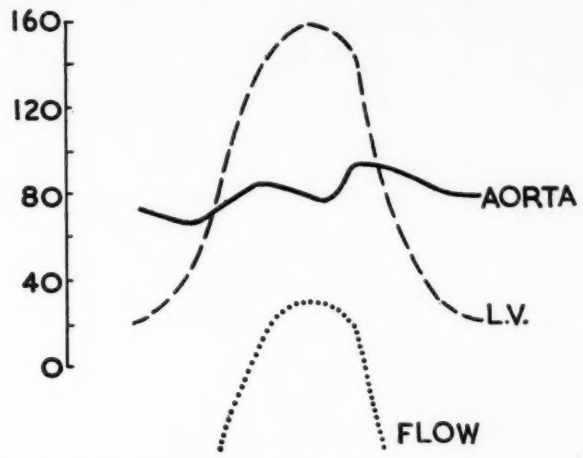

FIG. 2.—Superimposed left ventricular and aortic pressure pulses with flow curve derived from these from a case of aortic stenosis after significant aortic regurgitation had been produced by aortic valvotomy. A deep notch is present very near the summit of the aortic pressure pulse and synchronous with the peak of the flow curve.

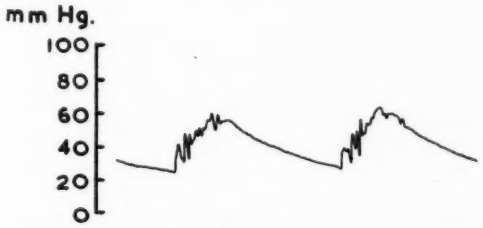

FIG. 3.—Aortic pressure pulse from a case of aortic stenosis, showing anacrotic notch and additional high-frequency vibrations on the upstroke.

These changes were associated with abbreviation of the aortic upstroke time so that it would be more accurate to state that the aortic systolic peak moved towards the anacrotic notch rather than vice versa. In a few cases, although the notch was situated higher on the upstroke after valvotomy, it was deeper than before, producing the appearance of the pulsus bisferiens. In these cases, there was clinical evidence of significant aortic regurgitation after the operation.

In all cases in which superimposed pressure pulses and a derived flow curve were studied, the anacrotic notch coincided precisely with the moment of maximum flow. It has been shown above that this coincidence is most unlikely to be due to over-estimation of the gradient at the nadir of the anacrotic notch.

DISCUSSION

The coincidence of maximum flow with the anacrotic notch was constant in this series. Study of simultaneous left ventricular and aortic pressure pulses recorded by left atrial and aortic catheterization and published by Wright *et al.* (1956) shows the same phenomenon. These observations

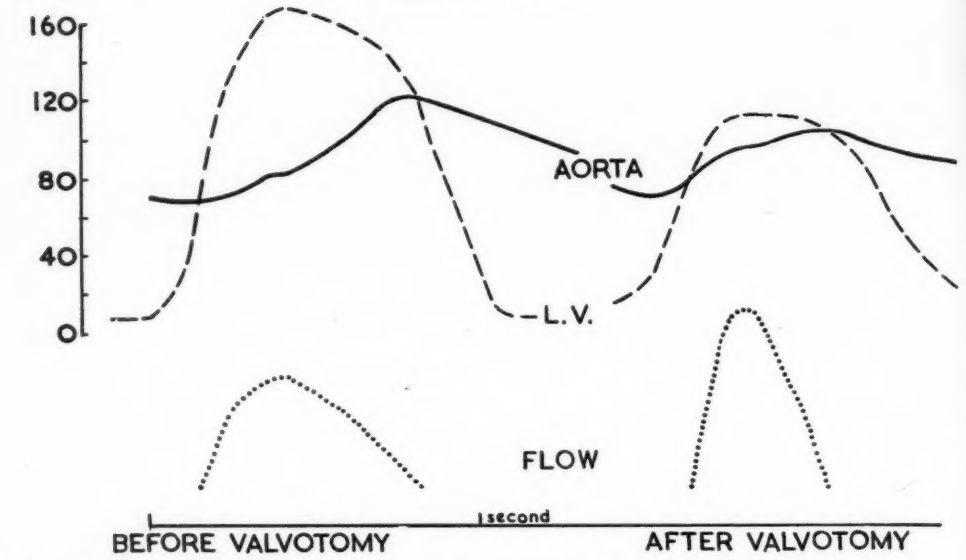

FIG. 4.—Superimposed left ventricular and aortic pressure pulses with flow curves derived from these from a case of aortic stenosis before and after aortic valvotomy. After valvotomy, there is abbreviation of the aortic upstroke time and the anacrotic notch is higher on the upstroke and less well-defined.

are considered to be good evidence in favour of the theory of Katz *et al.* (1927) that the notch is produced by the suction effect (Venturi) of the high-velocity blood stream.

Wiggers (1949) pointed out that the anacrotic notch is situated lower on the upstroke in severe cases of aortic stenosis than in milder cases. Katz *et al.* (1927) found in dogs that the left ventricular systolic peak tended to occur earlier than normal in severe aortic stenosis and this has been confirmed in man by Fleming and Gibson (1957). For this reason, combined with the delay in the aortic systolic peak, there is a long interval between maximum flow through the valve orifice and the attainment of maximum aortic pressure; a correspondingly long interval separates the anacrotic notch from the aortic peak. In a case of milder aortic stenosis or after a successful valvotomy (Fig. 4), there is a shorter interval between maximum flow and peak aortic pressure; the notch is situated nearer to the aortic peak and, therefore, higher on the upstroke. In addition, the reduced flow velocity, consequent on the increased size of the aortic orifice, produces a smaller suction effect and a less well-defined notch.

In the bisferiens type of pulse, a notch is present at or near the summit of the aortic pressure pulse and is yet of considerable depth. From the evidence presented above, the position of the notch suggests a relatively mild degree of stenosis and in the cases in which a pulsus bisferiens was found after valvotomy, there was also a satisfactory reduction in gradient. The depth of the notch, however, suggests a high flow velocity. The velocity of flow through an orifice depends, *inter alia*, on the size of the orifice and the volume of blood passing through it—the ventricular stroke volume in this case. In cases of atrial septal defect, the right ventricular stroke volume is often much above normal and Kjellberg *et al.* (1955) have emphasized the effect of the " pressure loss of velocity " on the form of the pulmonary arterial pressure pulse in this condition. In cases of atrial septal defect, a systolic gradient of 20–30 mm. Hg across the pulmonary valve may be found—a gradient that is no longer present after surgical closure of the defect (Brock, personal communication). Fig. 5 illustrates a case of atrial septal defect where the peak of the pulmonary arterial pressure pulse is deformed by a well-marked notch: in this case the right ventricular stroke volume was 250 ml. It

seems, therefore, that a high flow velocity, due to an increased stroke volume alone, is sufficient to produce a well-marked Venturi effect. A similar appearance is seen in the aortic pressure pulse in cases of persistent ductus arteriosus where the left ventricular stroke volume is abnormally large. Fig. 6 illustrates the effect of releasing a clamp on the ductus at operation: immediately the increased stroke volume and flow velocity produce a notch at the summit of the aortic pressure pulse.

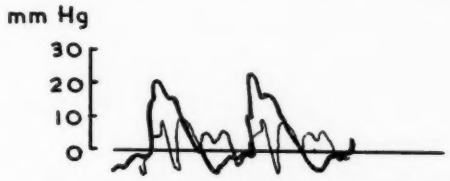

FIG. 5.—Tracing of superimposed right ventricular (thick line) and pulmonary arterial (thin line) pressure pulses from a case of atrial septal defect. The pulmonary arterial pressure pulse is deformed by a deep notch at its summit, due to the large right ventricular stroke volume (250 ml.) and high flow-velocity.

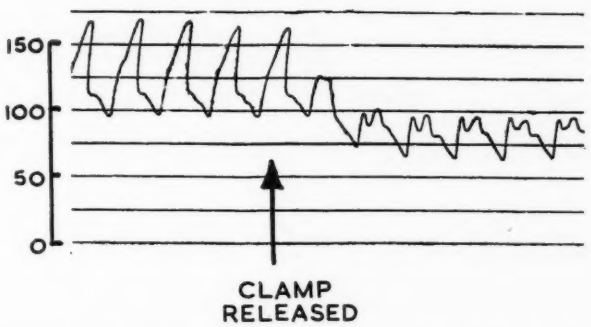

FIG. 6.—Aortic pressure pulse from a case of persistent ductus arteriosus. At the arrow a clamp on the ductus was released and a notch appeared on the summit of the pressure pulse, due to the increase in left ventricular stroke volume.

In cases with aortic regurgitation, the left ventricular stroke volume is increased by the amount of blood returning to the left ventricle in diastole. If there is, in addition, a mild degree of aortic stenosis, the flow velocity will be very high with little delay in the upstroke of the aortic pressure pulse. The notch produced by this high velocity will be situated on or near the summit of the aortic pressure pulse, which then has the form of the classical pulsus bisferiens of aortic stenosis and regurgitation (Fig. 2).

A further point of evidence against the concept of a reflected tidal wave is provided by comparison of the central and peripheral pulses in aortic valve disease. If part of the tidal wave is in fact reflected from the periphery, it should be possible to record this wave returning to the aorta in a peripheral arterial pressure pulse; this has not been done. It is considered, therefore, that the terms *percussion wave* and *tidal wave* are unacceptable, at least in this connection, and that the pulsus bisferiens does not consist of two separate waves but of a single wave split by a marked Venturi effect—the *quies media* of Galen. As the pulsus bisferiens indicates mild aortic stenosis with significant regurgitation, its presence is a contra-indication to aortic valvotomy.

Summary

Aortic and left ventricular pressure pulses recorded simultaneously at operation in 29 cases of aortic stenosis have been studied. A curve representing the changing gradient across the aortic valve has been derived from the superimposed pressure pulses; this curve has been used as an approximation to the curve of changing flow through the aortic orifice.

The anacrotic notch in the aortic pressure pulse is always found to be exactly synchronous with the moment of maximum flow, and it is suggested that the notch is produced by the suction effect of the high-velocity blood-stream.

In severe aortic stenosis, the position of the notch, low down on the upstroke, is shown to be related to the slow build-up of aortic pressure and the long interval between maximum flow through the aortic orifice and the aortic pressure peak.

The effect of a high flow-velocity produced by a large stroke volume alone is demonstrated by study of pulmonary arterial and aortic pressure pulses in atrial septal defect and persistent ductus arteriosus respectively. In both cases a well-defined notch is present at the summit of the pressure pulse.

The position of the notch in the pulsus bisferiens of combined aortic stenosis and regurgitation is interpreted as indicating only a slight delay in the aortic upstroke and therefore mild stenosis; its depth indicates a high flow velocity, due to the large stroke volume of aortic regurgitation. The presence of a pulsus bisferiens is, therefore, a contra-indication to aortic valvotomy.

Evidence from a comparison of central and peripheral arterial pressure pulses does not support the concept of a reflected component of the tidal wave and it is suggested that the anacrotic and bisferiens pulses do not consist of separate percussion and tidal waves, but are single waves deformed by the suction effect (Venturi effect) of a high-velocity blood stream.

All the operations were performed by Sir Russell Brock, to whom I am indebted for his co-operation in the recording of the pressure pulses.

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THE VALSALVA MANŒUVRE IN AORTIC VALVE DISEASE

BY

A. E. DOYLE* AND G. H. NEILSON†

From the Department of Medicine, Postgraduate Medical School, Hammersmith

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Since the introduction of aortic valvotomy, the assessment of aortic valve disease has become increasingly important. Studies of arterial pressure pulse tracings, although useful in diagnosis (Goldberg *et al.*, 1954) have proved disappointing in assessing the severity of stenosis (Gorlin and Case, 1956). It is noticeable that the systolic upstroke time varies in patients with atrial fibrillation, the variation being apparently related to change in pulse pressure (Goldberg *et al.*, 1954).

This communication reports the effects of the Valsalva manœuvre on the arterial pressure pulse curves of forty patients with aortic valve disease, with particular reference to the relationship between the variations in systolic upstroke time and pulse pressure.

Material and Methods

Femoral artery punctures were performed with local anæsthesia in forty patients using a No. 18 Cournand needle, connected by a short length of polythene tubing (bore 2·0 mm.) to a Statham 606 strain gauge. Pressure pulses were amplified by a two-stage D.C. amplifier, and recorded on an Elmqvist Triplex recording galvanometer. The frequency response of this system has already been reported (Bayliss *et al.*, 1950).

The needle was directed centrally and held in this position by the operator. Failure to do this resulted in tracing artefacts. The patient was asked to blow into a pressure bottle; the pressure achieved was measured by a mercury manometer. Straining was continued for at least ten seconds.

Pulse pressures, and the time from the beginning of the rise of the pressure pulse curve to systolic peak, were measured before and during the period of straining. Pressure pulses recorded during the overshoot (Sharpey-Shafer, 1953) were discarded; as will be discussed later, the relationship between systolic upstroke time and pulse pressure altered during the overshoot. Variations in pulse form occasionally led to difficulty in measurement of these factors.

The femoral pulse was recorded in forty patients. Twenty of these had aortic stenosis, either alone or with insignificant aortic incompetence. Ten others had aortic stenosis and incompetence; and the remaining ten had aortic incompetence alone.

All the patients with aortic stenosis had typical systolic ejection murmurs (Leatham, 1951). All had some clinical, radiological, or cardiographic evidence of left ventricular hypertrophy. None had systolic blood pressures greater than 150 mm. Hg. Two had faint aortic diastolic murmurs. Thirteen were regarded as severe: all these had considerable exertional dyspnœa, ten had angina of effort, and the cardiograms showed marked T wave inversion in twelve (Abdin, personal communication). Three died and autopsy revealed severe aortic stenosis in each; the other ten had aortic valvotomy, and systolic gradients across the aortic valve ranged between

* Present address: Department of Medicine, University of Melbourne, Victoria.
† Travelling Scholar, Royal Australasian College of Physicians. Present address: Department of Medicine, University of Queensland.

30 and 150 mm. Hg. The absence of simultaneous estimation of left ventricular stroke volume makes these measurements difficult to evaluate, as is obvious from the tracings obtained at operation shown in Fig. 1, in which the gradient varies between 5 and 60 mm. from beat to beat in a case

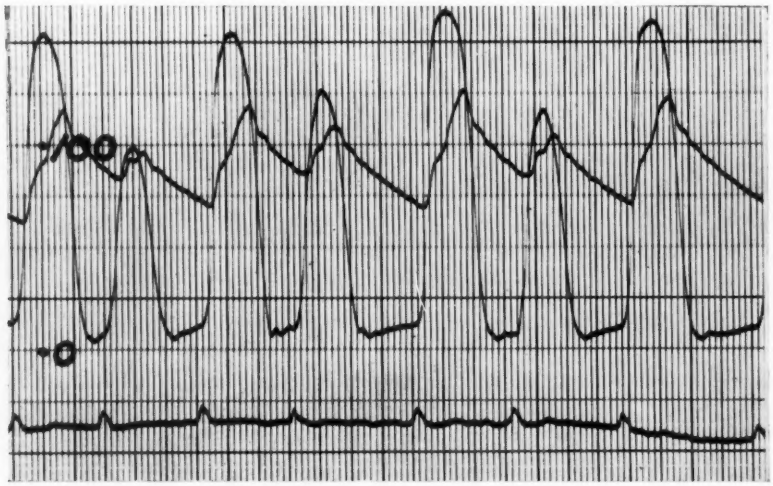

FIG. 1.—Variations of the gradient across the aortic valve in a patient with severe aortic stenosis and atrial fibrillation. The variations correspond with those in pulse pressure. Time marker interval 0·04 sec. Note also the variations in upstroke time in the aortic pulse.

with atrial fibrillation. Of the remaining seven, who were regarded as having mild or moderate aortic stenosis, two had angina of effort and dyspnœa on exertion, and one angina alone. Cardiographic changes were less in this group. In the severe group the resting systolic upstroke time ranged from 0·17 to 0·27 sec., and in the milder group from 0·14 to 0·22 sec. In the severe group the pulse pressure ranged from 35 to 70 mm., and in the milder group from 46 to 92 mm.

Ten other patients with the signs of aortic stenosis had loud aortic diastolic murmurs. In this group the resting systolic upstroke times ranged from 0·08 to 0·22 sec., and resting pulse pressures from 42 to 102 mm. In the remaining ten who had pure aortic incompetence, the resting systolic upstroke times ranged from 0·06 to 0·10 sec., and the resting pulse pressures from 41 to 117 mm.

RESULTS

The Resting Pulse Tracing in Aortic Valve Disease. The distribution of resting systolic upstroke times and pulse pressures in each group is shown in Fig. 2 and the relationship between the two measurements is shown in Fig. 3. Although patients with aortic stenosis tend to have low resting pulse pressures, and although those with severe stenosis more commonly have lower pulse pressures than those with milder stenosis or associated incompetence, there is nevertheless a considerable overlap between the groups. The systolic upstroke time seems to be constantly prolonged in severe stenosis, but is often prolonged to a comparable degree in less severe cases or in combined lesions also. By contrast the systolic upstroke time is constantly short in those with pure aortic incompetence; in this group also, however, the pulse pressure varies widely.

Changes in Pulse Form during and following the Valsalva Manœuvre. At the start of the period of straining both systolic and diastolic pressure rose and the pulse pressure remained unchanged,

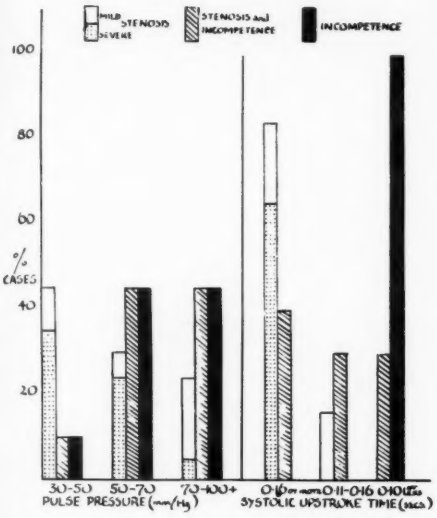

FIG. 2.—Distribution of systolic upstroke times and pulse pressures in resting arterial pulse tracings from 40 patients with aortic valve disease.

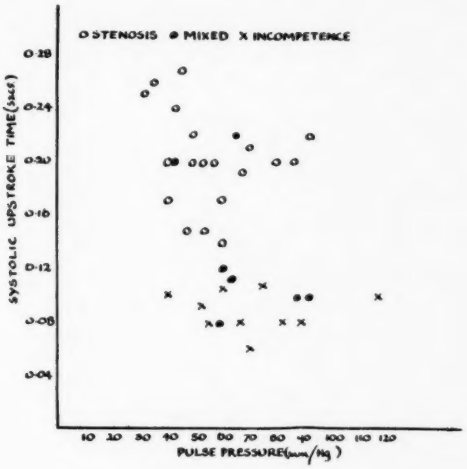

FIG. 3.—The relationship between systolic upstroke time and pulse pressure in resting arterial pulse tracings in 40 patients with aortic valve disease.

but after three to five pulses the systolic and diastolic pressures began to fall. The delay in the onset of the fall in pulse pressure was similar in aortic stenosis and in aortic incompetence: the fall in systolic pressure was greater than the fall in diastolic pressure so that the pulse pressure always fell. During this period the anacrotic notch, when present, initially remained at about the same height above the diastolic pressure, although towards the end of the straining period it usually fell (Fig. 4A). The fall in systolic pressure, occurring simultaneously, led to a reduction in the distance between the anacrotic notch and the systolic peak. Towards the end of the period of straining, when the falls in pulse pressure were maximal, the anacrotic notch disappeared. During the recovery phase patients in all three groups developed an overshoot, with a rise in pulse pressure, and as it rose the anacrotic notch reappeared and moved down the ascending limb of the pressure pulse curve.

In some resting tracings, two peaks were present. Their relative magnitude did not indicate whether the patient had stenosis, incompetence, or a combined lesion. During the straining period the second peak always became smaller, and usually formed a notch on the descending limb (Fig. 4B). Later it disappeared so that the pulse became single peaked, and during the overshoot this process was reversed. In three patients with aortic stenosis, one severe, the anacrotic notch moved towards the summit so that two equal peaks became evident: the second peak then became smaller as described above.

The Relationship between Changes in Pulse Pressure and in Systolic Upstroke Time. In those with aortic stenosis, the systolic upstroke time shortened when the pulse pressure fell during straining; in those with aortic incompetence it showed little consistent change. The changes in systolic upstroke time were similar when the changes in pulse pressure were due to atrial fibrillation.

The changes in systolic upstroke time for change in pulse pressure were measured. Two examples of the scatter of points so obtained are shown in Fig. 5. Regression lines of these changes were calculated for each patient, and the lines obtained in a group of seven patients with severe

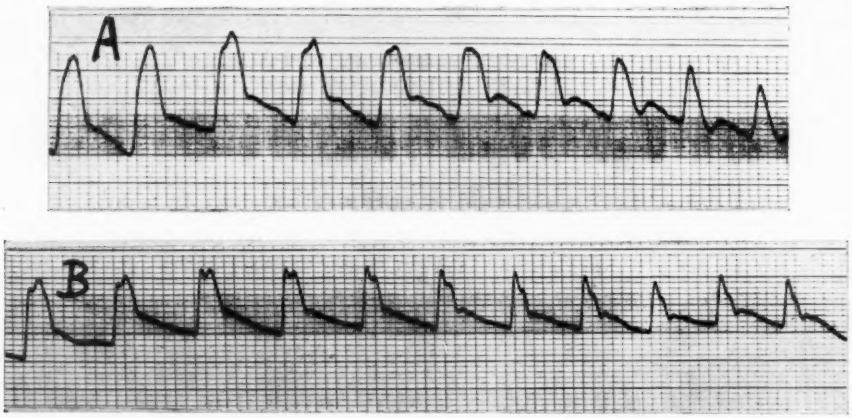

FIG. 4.—An example of the alteration in the pulse form during the Valsalva manœuvre in two patients, (A) with aortic stenosis and (B) with aortic stenosis and incompetence.

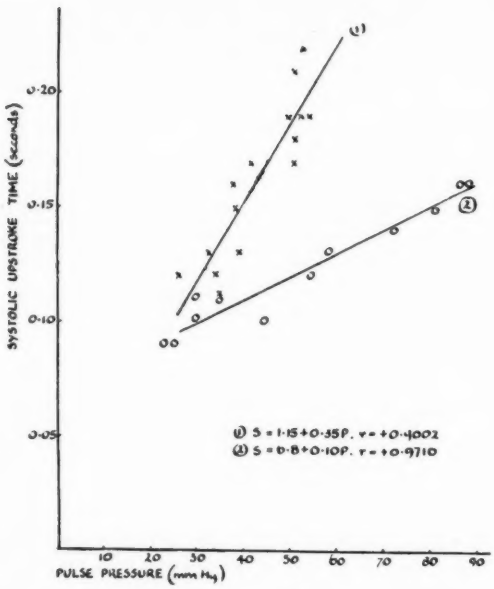

FIG. 5.—Examples of the scatter of points obtained by plotting pulse pressure against systolic upstroke time, (1) in a patient with severe aortic stenosis (coefficient of correlation +0·9002) and (2) in a patient with moderately severe aortic stenosis (coefficient of correlation +0·971). The regression formulae are shown, where S is systolic upstroke time and P the pulse pressure. The time unit of S is in 0·01 sec.

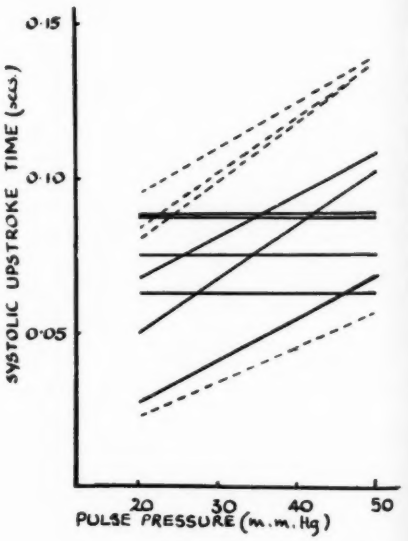

FIG. 6.—The regression lines of four patients with mild or moderately severe aortic stenosis (interrupted lines), and of seven patients with mixed aortic incompetence and stenosis (dark lines).

stenosis are shown in Fig. 7. In all the lines are steep, giving a large change in systolic upstroke time for change in pulse pressure. The lines obtained in a group of patients with aortic incompetence are contrasted in Fig. 7: they are very flat, being almost parallel to the pulse pressure axis, indicating that change of pulse pressure is associated with little or no change in systolic upstroke time in this group.

Four of the milder group with aortic stenosis, described above, were also studied in this way and the regression lines obtained are shown in Fig. 6. While not as steep as those found with severe aortic stenosis, they are not as flat as those found with aortic incompetence. Of the seven patients with mixed aortic stenosis and incompetence, four had flat regression lines resembling those found in subjects with aortic incompetence and three had lines resembling those of the patients with mild stenosis, being intermediate between those with severe stenosis and those with incompetence (Fig. 6).

In four patients, regression lines were obtained before and after aortic valvotomy (Fig. 8). In all four the slope of the regression line was much flatter after valvotomy than it had been before. In four other patients lines could be obtained only after operation: none were as steep as those obtained in the severe stenotic group. One line was flat; and it is of interest that severe aortic incompetence was present after the valvotomy in this patient: the other three were steeper, resembling those found with mild stenosis.

The Relationship between Change in Pulse Pressure and Rate of Systolic Upstroke. Variations in pulse form during the Valsalva manœuvre may lead to difficulty in measurement of the systolic upstroke time, particularly when a double summit is present. To overcome this we tried to determine whether the change in systolic upstroke time resulted solely from the change in pulse form

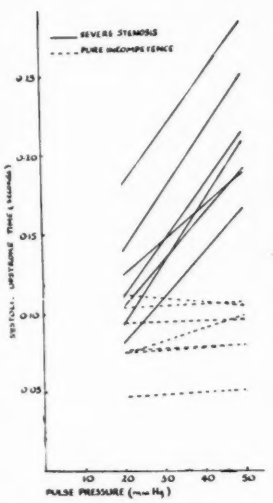

FIG. 7.—The regression lines of 7 patients with severe aortic stenosis, and 7 patients with aortic incompetence.

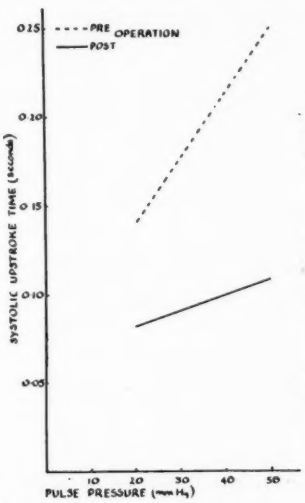

FIG. 8.—An example of the change in the regression line of a patient with severe aortic stenosis, following aortic valvotomy.

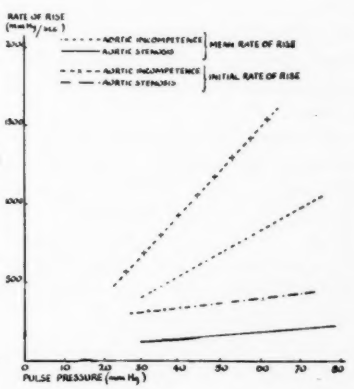

FIG. 9.—An example of the relationship between the *initial* rate of rise, and of the *mean* rate of rise of the pulse, and the pulse pressure in one patient with aortic stenosis and in one with aortic incompetence.

or partly also from the change in the rate of rise of the pulse wave. To do this the rate of rise in mm. Hg/sec. of the first 0·06 second of the pulse wave was compared with the mean rate from the start of the rise to the systolic peak, and the changes in these measurements that occurred with change in pulse pressure were also compared. The results indicate that when the pulse pressure changes, both the initial rate of rise and the mean rate of rise of the pulse wave alter in a similar manner. In aortic stenosis the rate of the pulse wave alters in a similar manner. In aortic stenosis the rate of rise alters much less for change in pulse pressure than it does in aortic incompetence. There is no doubt that the changes in pulse form, such as the disappearance of the second peak, are in part responsible for the reduction in systolic upstroke time with reduction of pulse pressure in aortic stenosis. There is equally no doubt, however, that the changes in pulse pressure also lead to changes in the speed of the upstroke of the pulse wave. The difference between patients with aortic stenosis and those with aortic incompetence, apply equally whether the initial rate of rise is measured or whether the total systolic upstroke is considered (Fig. 9).

Discussion

The results of this work indicate that arterial pulse tracings taken under resting conditions, have a limited value in the assessment of aortic valve disease. The systolic upstroke time is almost always prolonged in aortic stenosis, but may not differ much in those with severe and in those with moderate or mild stenosis. Similarly, the pulse pressure in severe aortic stenosis is often below 50 mm., but the occurrence of pulse pressures of this order in milder stenosis and the occasional finding of greater pulse pressures in the severe group diminish the value of the pulse pressure in the assessment of the severity of the stenosis.

The relationship between systolic upstroke time and the pulse pressure in resting tracings often fails to help in assessment of the severity of aortic stenosis. When, however, the pulse pressure changes, either because of atrial fibrillation or during the Valsalva manœuvre, the relationship between the changes in pulse pressure and the changes in systolic upstroke time seems to be of value in determining whether the stenosis is severe or whether it is mild or associated with significant incompetence. In general, the greater the change in upstroke time for a given change in pulse pressure, the more severe is the stenosis likely to be. When this relationship is expressed as a regression line, the lines of those with severe stenosis are much steeper than the lines of the milder cases, and there is little overlap between the two groups. Furthermore, following aortic valvotomy the slope of the regression line is much flatter than before the operation, even when the resting upstroke time is little reduced.

Probably the fall of pulse pressure during the Valsalva manœuvre is due to the fall in stroke volume. In support of this is the fact that regression lines obtained in the same subject are almost identical, whether the variations of pulse pressure are due to atrial fibrillation or to the fall in pressure during the Valsalva manœuvre. If the variations in pulse pressure reflect changes in stroke volume, the linear relationship between change in systolic upstroke time and change in pulse pressure, and the apparent relationship between the slope of the regression line and the degree of aortic valve resistance suggest that the systolic upstroke time is a resultant of the stroke volume and valve resistance.

It must be emphasized, however, that although variations in pulse pressure in individual subjects probably reflect changes in stroke volume, differences in pulse pressures between different subjects cannot be taken to indicate corresponding differences in stroke volume; other factors such as aortic pressure-volume characteristics and the peripheral resistance also influence pulse pressure. These factors probably account for the lack of correlation between resting upstroke time, or resting pulse pressure, and the severity of the stenosis. They also affect the slope of the regression line in aortic stenosis, for the slope is steeper during the straining period than during the overshoot, probably because of the difference in peripheral resistance during the two periods. Another factor that must be taken into account is change of heart rate; it seems likely that alteration in rate would lead to variation in upstroke time by changing left ventricular stroke output.

The changes in pulse form that occur during the Valsalva manœuvre are of great interest. Goldberg *et al.* (1954) noted similar changes and ascribed them to change in pulse pressure. We believe that they are at least partly due to changes in peripheral vascular resistance, for pulses of identical magnitude recorded at different stages of the Valsalva manœuvre are often of very different form. Whatever their significance these variations suggest that the form of the pulse tracing in resting tracings may not be a reliable guide to the nature of the valve disease present, for the same subject may exhibit successively an anacrotic notch, a double summit pulse, and a smooth single peak. For these reasons no absolute value can be estimated for the slope of the regression line in severe aortic stenosis. Using the line obtained during the fall in pulse pressure, all the patients with severe stenosis had steep regression lines, giving a change in upstroke time of 0·10 sec. or more for a change of 50 mm. Hg in pulse pressure.

The delay in the fall in pulse pressure during the straining period, which was regarded by Gorlin and Case (1956) as characteristic of aortic stenosis, has not been evident in our patients; the delay in the onset of the fall was similar in those with mild or severe stenosis and in those with aortic incompetence. Our results differ also from those of Hamilton *et al.* (1936) in that all patients with aortic incompetence studied developed an overshoot after straining. We can offer no explanation for the difference between their results and ours, but it is of interest that Goldberg *et al.* (1954) noted that some with aortic incompetence developed overshoot responses after straining.

In spite of the theoretical complexities of the relationship between pulse pressure and upstroke time, the relationship between the changes in the two measurements seem useful as an index of severity of aortic stenosis. This information cannot be reliably deduced from resting pulse tracings, and even the measurement of the gradient across the aortic valve (Goldberg *et al.*, 1955) may be misleading in the presence of high or low left ventricular stroke volumes or in the presence of atrial fibrillation. We believe that the method of assessment reported here compares favourably in simplicity and accuracy with other methods at present available for the assessment of aortic valve function.

Summary and Conclusions

Although in aortic stenosis the systolic upstroke time is usually prolonged and the pulse pressure often low, neither measurement alone correlates well with the severity of stenosis.

The Valsalva manœuvre leads to variation in the pulse form. The shape of the pulse is an unreliable guide to the relative dominance of stenosis or incompetence.

Variations in pulse pressure during the Valsalva manœuvre or in atrial fibrillation and variations of upstroke time in the same pulses have a linear relationship. In severe stenosis the upstroke time changes more than in milder stenosis for a given change in pulse pressure. The relationship provides an index of severity of stenosis.

We are indebted to Dr. J. F. Goodwin for permission to study the patients under his care and for much helpful advice and criticism, and to Dr. Max Zoob for permission to use Fig. 1. We wish to thank Dr. Paul Wood and Professor J. McMichael who read the manuscript and offered much helpful advice.

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PULMONARY OSSIFICATION WITH CARDIAC CALCIFICATION IN MITRAL VALVE DISEASE

BY

H. A. FLEMING* AND C. L. N. ROBINSON

From Sully Hospital, Glamorgan

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Our purpose is to present eight cases of mitral valve disease with disseminated pulmonary ossification, in seven of which there was also massive calcification of the mitral valve or left atrium or both. Of these five were seen by us at this hospital and are the only cases of pulmonary ossification in association with mitral valve disease that have been seen here up to the present: the other three were studied from their records.

Pulmonary ossification is rare and cardiac calcification not common, and the combination of the two must be unusual. Wagner in 1859 first reported bone formation in the lungs in a woman aged 25 years with dropsy. Salinger (1932) first recognized the relation of bony nodules to mitral valve disease and reported a second case. Other reports have been made by Wells and Dunlap in 1943 (1 case) and by Grishman and Kane in 1945 (8 cases). Elkeles and Glynn (1946) described the first case in England. In 1947 Elkeles reported a further case in which the appearances are very different from all other cases: it would appear from the radiograph to be almost certainly a case of calcified pulmonary tuberculosis. Later reports have been made by Lawson (1949), Lendrum *et al.* (1950, 3 cases), Sahn and Levine (1950), Kerley, (1951), Schinz *et al.* (1953), Steiner and Goodwin (1954, 2 cases), and Short (1955) (1 case each unless stated). In many of these reports the condition is referred to in passing, and the clinical and pathological details are often very few. Whitaker *et al.* (1955) presenting 7 new cases in detail, give an excellent review and a discussion of the ætiology.

Calcification of the mitral valve is common in mitral valve disease and is recorded in all recent series. For example Wood (1954) reported some degree of calcification in 28 per cent of cases submitted to mitral valvotomy and heavy calcification in 50 per cent of those with a significant degree of mitral incompetence.

Calcification of the left atrium was first described radiologically by Shanks *et al.* (1938). Ruskin and Samuel (1952) reviewed the only 18 cases they found described in life and added 2 new ones: they view it as a rare condition usually associated with mitral valve disease. The calcification is subendocardial and varies from isolated plaques in the posterior wall to involvement of the entire atrial wall, and in some cases the mitral valve was also calcified. Steiner and Goodwin (1954) mention 2 in a series of 91 cases. The relevant features of our cases are summarized in Table 1.

All the patients except Case 4 were submitted to operation for mitral valvotomy. (Cases 1, 2, and 3 by Mr. Dillwyn Thomas, Case 5 by Mr. H. R. S. Harley, Case 7 by Mr. O. S. Tubbs, and Cases 6 and 8 by Mr. Ian Hill.) In all the operated cases the areas of ossification could be easily felt in the lung substance.

Case 1 (Fig. 3) is of interest in that the entire wall of the left atrium was calcified and this process extended along all the pulmonary veins so that no access to the mitral valve was possible by the accepted methods of the time. The calcium appeared to be within the wall rather than in thrombus.

* Present address: Brompton Hospital, London, S.W.3.

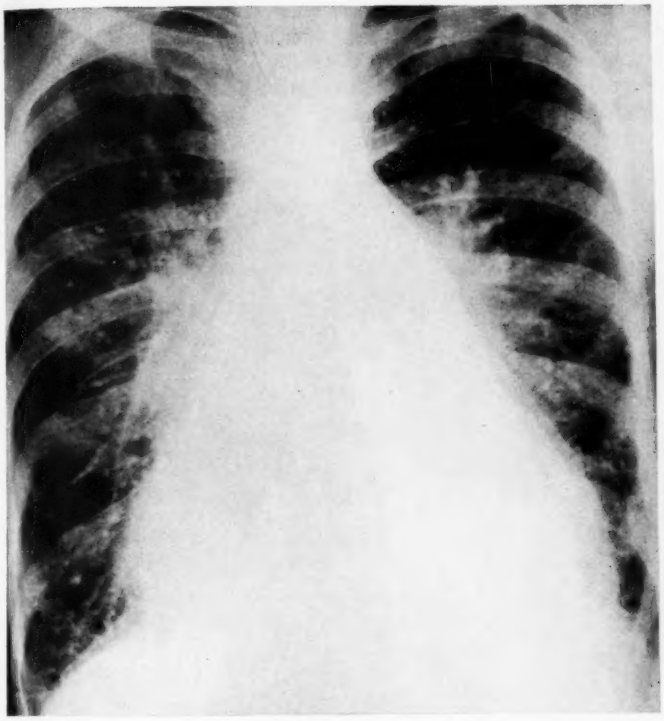

FIG. 1.—Case 1. P.A. chest radiograph, showing the features of pulmonary hypertension and the interlobular septa that were seen in all cases. The pulmonary ossification is most obvious in the right lower zone.

FIG. 2.—Case 1. Detail of the radiograph of the right lower zone, showing the interlobular speta and the inconspicuous pulmonary arteries.

TABLE I

DETAILS OF CASES. No patient had suffered any symptoms of left-sided heart failure, all of them showed marked interlobar septal lines and all had evidence of a raised pulmonary vascular resistance. None of them had radiological hæmosiderosis.

Case No.	Sex and age	Age of chorea or rheumatic fever	P.A.P. mm. Hg	Hæmoptysis	Mitral syst. murmur	Congestive heart failure	Calcium in heart	Bone in lungs	Maximum diameter of lung bone	Lung biopsy	Hæmosiderin present at biopsy
1	M. 24	8, 12, 16	80/60	—	±	+	L.A.	All zones, espec. R.L.Z.	6 mm.	Bone	±
2	M. 30	—	90/30	—	−	+	M.V.	,, ,,	5 mm.	Bone	−
3	M. 40	18, 20	125/50	for 14 yr.	−	−	L.A.	,, ,,	7 mm.	Bone	−
4	M. 49	10, 11	—	—	±	−	L.A. & M.V.	,, ,,	5 mm.	N.D.	N.D.
5	M. 34	—	100/50	small, yr. ago	±	−	M.V.	,, ,,	4 mm.	Bone	−
6	M. 35	—	52	9 and 7, yr. ago	±	+	M.V.	,, ,,	3 mm.	Bone	±
7	M. 33	16	50	slight 4 mo. ago	−	−	M.V.	All zones except L.U.Z.	4 mm.	N.D.	N.D.
8	F. 34	10	50	—	−	−	Nil.	Both lower & mid. zones, espec. R.L.Z.	3 mm.	N.D.	N.D.

L.A. Left atrium. M.V. Mitral valve. N.D. Not done.
R.L.Z. Right lower zone. P.A.P. Pulmonary artery pressure (in mm. Hg). In Cases 1, 2, 3, and 5 the pressures are as recorded at
L.U.Z. Left upper zone. catheterization and in Cases 6, 7, and 8 they are means recorded at thoracotomy.

Case 3 had worked as a miner from the age of 14 to 18 years when he was told that he must no longer work: this he had obeyed for 22 years and by the time we saw him he was greatly disabled. In spite of the apparently unpromising situation (Table I and Fig. 4 and 5), within two months of valvotomy he had evidence of a much lower pulmonary vascular resistance and was working for the first time for 22 years.

Three cases had been in right-sided heart failure and had been treated for this. The other

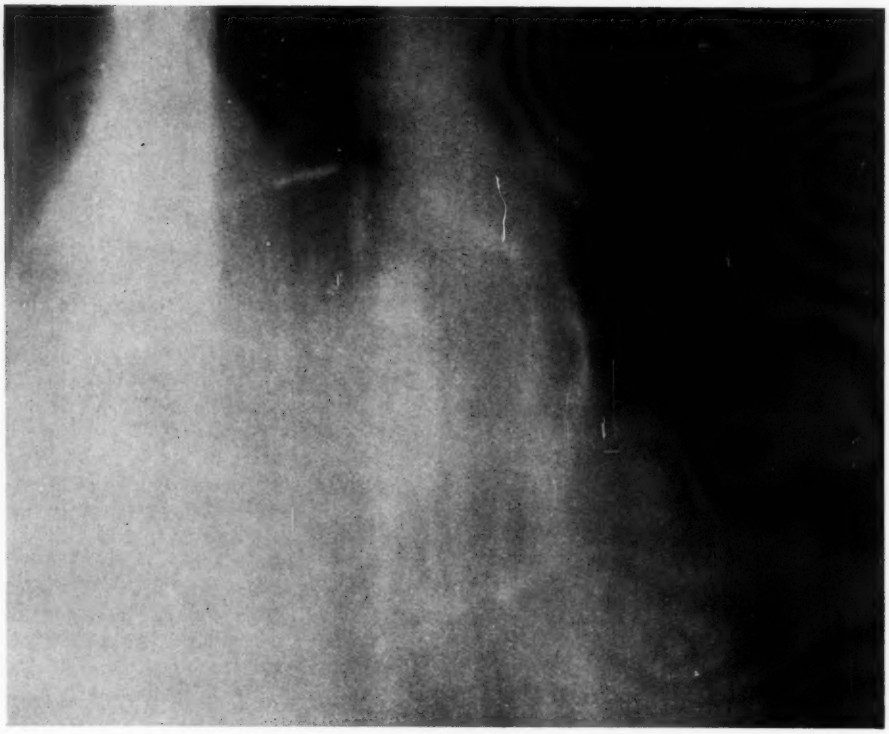

FIG. 3.—Case 1. Tomograph in the right anterior oblique position, showing sheet of calcium in the left atrial wall.

five had not been so treated over a long period and it is unlikely that the treatment made any positive contribution to the appearance of the calcification.

The absence of clinical left-sided heart failure was judged by the complete lack of cardiac asthma, paroxysmal nocturnal dyspnœa, and orthopnœa in each case.

Interlobular septal lines (Kerley's B lines) were clearly visible in all cases on the P.A. radiograph. No attempt has been made to assess these quantitatively as great differences in appearance can be produced by variations in radiological technique. They were always much more prominent than in average cases of mitral stenosis.

Pulmonary vascular resistance was judged on clinical, radiological, and cardiographic grounds as described by Wood (1954) or on the pressures recorded at catheterization or operation (Table I). In Cases 1, 2, and 5 histology of the pulmonary arterioles in the biopsy also showed changes of pulmonary hypertension. In Cases 3 and 6 no suitable vessels were seen in the material. In all cases the evidence in favour of a high resistance was strong. The cardiographic changes of

right ventricular hypertrophy were extreme: the radiographs when shown to an experienced observer were all reported as high resistance mitral disease, and the surgeons found much right ventricular hypertrophy and dilatation of the pulmonary artery. Indirect left atrial pressure could only be obtained in Case 2 (mean 18 mm. Hg) so resistances were not calculated, but they were obviously extreme, with high pulmonary arterial pressures and low cardiac outputs.

Hæmoptysis was not a conspicuous feature except in Case 3 who had had frequent hæmoptyses for 14 years. The areas of ossification were particularly striking in this case (Fig. 4 and 5). Cases 5 and 6 had small hæmoptyses some years previously, and Case 7 four months previously, but the other four had never coughed blood.

No case had evidence of disease in valves other than the mitral. In four there was a mild mitral systolic murmur but in none was this judged to represent significant mitral incompetence. This conclusion was fully supported by the surgical findings.

All cases except the woman had gross calcification in the heart. This was seen on fluoroscopy and was studied and confirmed by tomography and at operation. In four it was in the mitral valve, in two in the left atrium, and in one in both. It was always easily seen. Case 1 (Fig. 3), showed the left atrial calcification most strikingly; in Case 3 it was in the superior portion of the wall and in Case 4 it encircled the superior and posterior walls.

The pulmonary ossification was usually evident in all zones of the lungs but was always most dense in the lower zones especially on the right, and least prominent in the upper zones particularly the left. The shadows were irregular in outline and size and varied from barely visible to up to 3 mm. in diameter in all cases. In most they were also larger than this (Table I) and in Case 3 were up to 7 mm. in diameter (Fig. 5).

Hæmosiderosis was not seen radiologically in any case, nor was it diagnosed in the biopsy in the five examined. In two of them small amounts of hæmosiderin were present in the lung around the bone, in macrophages usually. The nodules were found to be of bone in each of the five where biopsy was made. All the patients are still living and there is no evidence of the state of the calcium in the heart, but it did not appear to differ from the calcium found in other cases of rheumatic valvular disease.

Differential Diagnosis

The presence of small, irregular, calcified lesions, diffusely spread throughout the lower and middle zones of both lungs in a male patient with clinical and radiological signs of mitral valve disease and pulmonary hypertension should obviate a diagnosis of any other cause for the calcification.

Among such other types is a coarse branched form of ossification of unknown ætiology, affecting predominantly elderly men in the lower zones of both lungs (Schinz *et al.*, 1953); it occurs in interstitial tissue. Again, *Microlithiasis alveolaris pulmonum* (Puhr, 1933) is a sequel to chronic inflammation, causes a large number of fine nodules in both lungs with least involvement of the apices, and may be so extensive as to cause death from respiratory failure. The texture of the lung at autopsy is like that of pumice stone and the sawn surface feels like sandpaper. The tiny concretions occur in alveoli and may be washed out like grains of sand.

The calcification of miliary tuberculosis is finer and more diffuse and affects all lung zones. The distribution and character of calcification in other forms of pulmonary tuberculosis is distinctive. Infection with *Histoplasma capsulatum* may cause fine diffuse calcification in both lungs, but this and infection with *Coccidiodes immitis* occur endemically, and each may be confirmed by specific laboratory investigations. Other opacities that need differentiation include those of sarcoidosis, leukæmia, Hodgkin's disease, pneumoconiosis, hæmosiderosis, and lymphangitis carcinomatosa.

Pathology

The pathological features of the bone in our five cases that were biopsied are similar to those already reported by Elkeles and Glynn (1946) and Whitaker *et al.* (1955). The bone is of the

woven type, is intra-alveolar, and may contain bone marrow. Because of the identical X-ray and operation findings in our other three that had no biopsy, it seems reasonable to suppose that the changes were the same. The nodules in our Case 3 (Fig. 5) are unusually numerous and measured up to 7 mm. in diameter. Hæmosiderin was an inconspicuous feature of the biopsies and we have

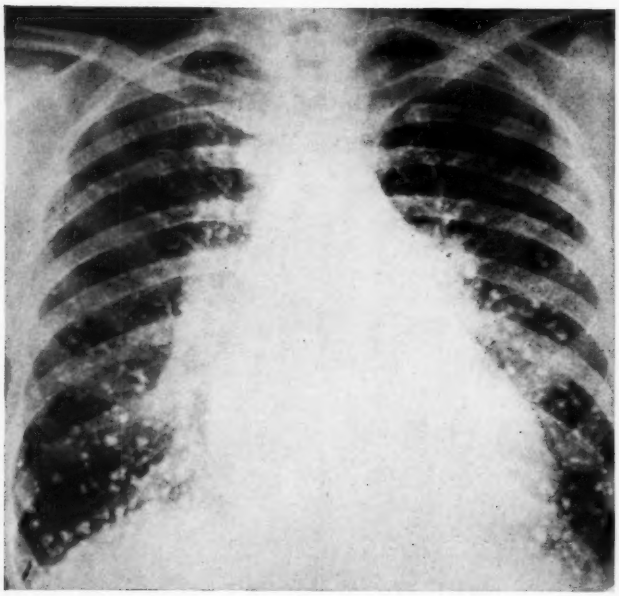

FIG. 4.—Case 3. P.A. chest radiograph, showing features of pulmonary hypertension and the unusually large and numerous areas of ossification of wide distribution. The left upper zone is least involved and the right lower zone most involved.

FIG. 5.—Case 3. Detail of the radiograph of the right lower zone, showing the largest and the most numerous areas of ossification. In this penetrated film the lines of the interlobular septa which were present are not apparent.

therefore no evidence to support Lawson (1949) and Ellman and Gee (1951) who suggest that there may be a relationship between hæmosiderosis and pulmonary ossification. The concentration and size of the nodules tended to be greatest in the lower lobes, especially on the right, but was sometimes almost universal as in Case 3 (Fig. 4). The upper lobes were least involved, particularly the left.

CLINICAL AND RADIOLOGICAL FEATURES

The ages of our patients ranged from 24 to 49 years. The incidence of rheumatic fever (5 of 8 cases) was similar to that reported in cases of pure mitral stenosis (Wood, 1954).

It is interesting that 7 of our 8 cases were men. The woman (Case 8) had pulmonary ossification and the other clinical features, but she was lacking in intracardiac calcification. Whitaker *et al.* (1955) had only one woman among their 7 cases, and a high incidence of men is found throughout the reports of pulmonary ossification in mitral valve disease. Considering the relatively greater frequency of mitral stenosis in women, this probably represents a much higher incidence of the condition in men.

We have no studies of calcium or hormone metabolism in our patients, but note that Allbright (1947) produces evidence of the influence of sex hormones on bone formation. Sparks *et al.* (1955) and Lostroh and Choh Hao Li (1955) have made interesting observations on the effects in

the mouse of cortisone on the deposition of calcium in various viscera, including the heart. Though they have not found these deposits in the lung (Lostroh, 1956) it is possible that their work may prove to have some bearing on the subject. Further than to suggest that pulmonary ossification and massive deposits of calcium in the heart may be the result of steroid stimulation, we have nothing further to offer and discussion will be limited to the pulmonary ossification. The first case of Whitaker *et al.* (1955) a man, aged 30, with calcific mitral and aortic stenosis would fit into our group. The high incidence of gross calcification of the mitral valve is noteworthy in our group. In surgical cases Wood (1954) found moderate or heavy calcification in only 12 per cent and most of these had significant incompetence, a feature entirely lacking in our cases where gross mitral calcification was present in 5 of the 8 cases.

Hæmoptysis. Hæmoptysis in mitral stenosis may be of five different kinds (Wood, 1954) and it is likely that our cases could, at times, have been liable to most of these. In retrospect it is impossible to classify this symptom and to compare it with the reported incidences. Hæmoptysis was a striking feature in one only, though it had occurred in minor degree in three others. It is recognized that hæmosiderosis can be found without overt hæmoptysis, but there was no radiological or biopsy evidence of hæmosiderosis in this group. Hæmoptysis has not been a feature of most previous reports of pulmonary ossification.

Pulmonary Venous Congestion. None of our cases had at any time suffered symptoms of pulmonary venous congestion but all showed well marked transverse interlobular lines in the lower lobe of each lung. These we interpret as meaning that at some time these patients had suffered from a raised left atrial pressure with pulmonary venous congestion. These lines were first radiologically described by Kerley (1933) and have caused increasing interest in recent years when they have been the subject of numerous reports, e.g. Fleischner and Reiner (1954) and Short (1955). While some workers (Whitaker and Lodge, 1953; Goodwin *et al.*, 1955) have sought to relate their occurrence to the presence of pulmonary arterial hypertension, there is now good evidence (Carmichael *et al.*, 1954; Bruwer *et al.*, 1955; Gough, 1956; and Rossall and Gunning, 1956) to suggest strongly that the important factor in mitral valve disease is the rise of pulmonary venous pressure. We agree with Grainger and Hearn (1955) that conditions such as mediastinal reticulosis or neoplasms, sarcoidosis, and pneumoconiosis can produce these lines and, in addition, we have observed them following hæmoptysis and during the use of lateral recumbency for tuberculous cavity closure. In mitral valve disease the transient lines would appear to be due to œdema of the interlobular septa while the more permanent type may be due to hæmosiderin deposition or to chronic fibrous thickening of the septa. In each case there is good evidence that, at the time of their production at least, there is a raised pulmonary venous pressure. Such lines are not easy to reproduce in figures particularly as the penetration most suitable for their demonstration is not best suited to showing pulmonary ossification. However, careful perusal of the radiographs reproduced in various papers on pulmonary ossification already mentioned shows these lines to be present commonly. This is certainly so in Cases 5 and 7 and probably in Case 3 of Whitaker *et al.* (1955).

Pulmonary Vascular Resistance. Clinical evidence of raised pulmonary vascular resistance was present in all our cases, and the level of the pulmonary artery pressure was measured at catheterization in four and at operation in another three (Table I). In the seven cases of Whitaker *et al.* (1955) there was clinical evidence of pulmonary hypertension in six, and in the seventh there was cardiographic evidence of right ventricular hypertrophy. In all other cases of pulmonary ossification where there are sufficient details published there is good evidence of severe pulmonary hypertension. This is true even in the early reports of Elkeles and Glynn (1946) where the radiograph suggests pulmonary hypertension and, as Heath and Whitaker (1955) have already suggested, the histological changes they interpreted as rheumatic arteritis were probably those of fibrinoid necrosis associated with pulmonary hypertension.

While we would agree with the concept of Wood (1954) that most patients with a very high pulmonary vascular resistance have never had any symptoms of pulmonary venous congestion and developed their extreme resistance at a relatively early stage in the course of the disease, we do feel

that the present small group of cases forms an exception. There is evidence in the transverse lines that there had been pulmonary venous congestion and yet when seen they had severe pulmonary hypertension. Whitaker *et al.* (1955) have also made this suggestion but without amplification or mention of the horizontal lines. We would therefore agree with the suggestion of Lendrum *et al.* (1950) that the ossification develops in areas of pulmonary œdema, the œdema in our cases being sub-clinical. Whether the development of pulmonary hypertension with narrowing of the arterioles and diminution of blood flow has any direct bearing on this is difficult to say. In other areas of the body local ischæmia promotes calcification, but with the double blood supply to the lungs the explanation is unlikely to be so simple. It is of interest that the ossification in the lungs is always greatest in the lower zones where the narrowing of the pulmonary arteries is most pronounced. This similar distribution suggests that the two findings may be related. It is possible that the secondary development of a raised pulmonary vascular resistance in these cases merely permits a sufficiently long survival after asymptomatic pulmonary œdema to allow ossification to occur.

Summary

Eight new cases of pulmonary ossification in mitral stenosis are reported: seven were men who had also massive calcification in the mitral valve or the left atrium. The possible influence of steroids is discussed.

These 8 cases and many of those previously reported had severe pulmonary hypertension and well-marked interlobular septal lines in the lower zones. It is suggested that pulmonary ossification develops in a small group of patients, the natural history of whose disease includes both subclinical pulmonary œdema and elevation of the pulmonary vascular resistance.

We would like to thank Mr. Dillwyn, Mr. E. Thomas, Mr. H. R. S. Harley, Dr. L. R. West, and Dr. H. M. Foreman of Sully Hospital, under whose care Cases 1, 2, 3, and 5 were investigated and treated. Dr. P. E. Dipple kindly allowed us to see Case 4. Dr. G. Simon drew our attention to Cases 6, 7, and 8, and Dr. C. Baker, Dr. G. Hayward, Mr. O. S. Tubbs, and Mr. Ian Hill were kind enough to give us access to their records of these cases. We are grateful to Mrs. B. Marshall for the photographs and Miss P. Edwards for secretarial assistance.

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MYOCARDIAL FIBROSIS AND CALCAREOUS EMBOLI IN VALVULAR HEART DISEASE

BY

E. D. WIGLE*

From the Department of Pathology, Postgraduate Medical School, London

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In the past decade the great advances of cardiac surgery have focused new attention on aortic and mitral valve disease. The investigation of these cases by clinical and technical means has been the subject of increased interest (Wood, 1954; Gorlin *et al.*, 1955). Study of the pathology of the mitral and aortic valves has correspondingly increased (Brock, 1952). The observation that myocardial fibrosis is unduly frequent and occasionally extensive in cases of congenital and acquired aortic stenosis with little or no coronary artery disease has often been made (Friedberg, 1949; Marquis and Long, 1955). The occurrence of angina pectoris, the electrocardiographic changes on exercise and the liability to sudden death in these cases have led these authors and others to suggest that the myocardial fibrosis is due to myocardial ischæmia as a result of functional coronary insufficiency. In addition, in cases of mitral stenosis, the occurrence of angina pectoris and the cardiographic changes on exercise have been attributed to myocardial ischæmia as a result of functional coronary insufficiency (Wood; Stuckey, 1955). In an attempt to determine how much myocardial fibrosis that is, not attributable to coronary disease or to rheumatic myocarditis, and therefore possibly due to functional coronary insufficiency, may occur in these two groups, seven cases of aortic stenosis and seven cases of mitral stenosis (with and without regurgitation) were studied post mortem by a method combining a coronary artery injection technique with careful examination of the myocardium. The necropsy findings of a large number of cases of both aortic and mitral stenosis were also reviewed. The amount of myocardial fibrosis noted in the two groups together with the finding of previously undescribed arterial lesions prompt this report of the results.

METHOD

At necropsy the hearts were carefully dissected, cleared of any clots, and weighed. Shortly thereafter (usually within three hours), the coronary arteries were cannulated under water at 37° C. and perfused with water of the same temperature until the washings returned clear from the coronary sinus. Approximately 100 ml. of 15 per cent formol-calcium were then injected in order to fix the musculature, followed by 10 to 20 ml. of warm water (to prevent mixing of the formol-calcium and the barium gelatine). Warmed barium-gelatine, prepared according to the technique of Gross (1921), was then injected into the arteries at a pressure of 140 mm. Hg. The heart was placed in iced water until the gelatine had set, and an X-ray was taken. Following this the heart was placed in a solution of 15 per cent formol-calcium for further fixation for at least one week. Dissection of the heart was then carried out. Using the radiograph as a guide the coronary arteries were sectioned at 3–4 mm. intervals in order to extend, by gross and microscopic examination, the X-ray findings. The heart muscle was then sliced from apex to base at 5-mm. intervals and the slices examined under a magnifying lens. The position, appearance, and size of any myocardial lesion were recorded, blocks being taken from the abnormal areas for microscopic examination. In addition blocks were taken

* During the tenure of a British Council Scholarship. Present address : Toronto General Hospital, Toronto ,Ontario, Canada.

from muscle of normal appearance from the postero-basal and antero-apical regions of the left and right ventricles.

Interpretation

Coronary Atheroma. In the dissection of the coronary arteries some areas of atheroma were found that had failed to cause coronary narrowing in the radiographs of the injected hearts. Such atheromatous areas were at times seen to narrow the lumina of vessels by up to one-quarter of their diameters when compared with adjacent portions of the same vessels, but at other times did not cause any narrowing of the vessel lumina at all. It has been noted previously that atheroma does not necessarily cause coronary narrowing (Stewart *et al.*, 1935). As a result of the above findings it has been found convenient to grade coronary artery disease in the following manner.

Grade I: No coronary narrowing either on dissection or in the radiograph.
Grade II: Narrowing up to one-quarter of the diameter of the vessel lumen on dissection, but no radiographic evidence of coronary narrowing.
Grade III: Narrowing of between one-quarter and one-half of the diameter of the vessel lumen on dissection, associated with coronary narrowing in the radiograph.
Grade IV: Narrowing of greater than one-half of the diameter of the vessel lumen on dissection or in the radiograph.
Grade V: Complete obstruction of the vessel lumen.

No occluding coronary thrombus was found.

In Tables I and II the grade of atheroma recorded represents the most severe degree of atheroma found in any of the coronary arteries of that case. In the six cases with Grade I coronary atheroma there were at most two intimal collections of cholesterol. For the purposes of the description and discussion that follow the coronary arteries of this group are considered as having normal lumina.

Size of Coronary Arteries. At every examination the three major coronary arteries (left anterior descending, left circumflex, and right) were measured near their origins. From their diameters their total cross-sectional areas were calculated (Table I and II) and plotted against the weight of the heart.

TABLE I

Coronary Atheroma and Myocardial Fibrosis in Seven Cases of Mitral Stenosis with or without Incompetence

Case No.	Age	Sex	Valve lesion	Valve circ. (mm.)	Heart wt.	Total coronary bore (sq. mm.)	Coronary atheroma	Macroscopic fibrosis			
								M.I.	I.F.	L.F.F.S.	S.F.F.S.
1	63	F	M.S.†	60	480	45·0	IV	1	0	0	0
2	39	F	M.S.	55	310	34·8	I	0	0	0	3
3	32	M	M.S.	40	456	44·8	I	0	0	0	0
4	52	F	M.S.	35	338	38·0	0*	0	0	0	5
5	55	F	M.S. M.R.‡	50	527	63·7	II	0	0	0	3
6	56	F	M.S. M.R.	60	495	32·0	0	0	0	0	2
7	57	M	M.S. M.R.	50	615	63·0	II	1	0	0	2

* See text.
† Mitral stenosis.
‡ Mitral regurgitation.

M.I. = myocardial infarct.
I.F. = interstitial fibrosis.
L.F.F.S. = large focal fibrous scar.
S.F.F.S. = small focal fibrous scar.

TABLE II

CORONARY ATHEROMA AND MYOCARDIAL FIBROSIS IN SEVEN CASES OF AORTIC STENOSIS, WITH OR WITHOUT INCOMPETENCE

Case No.	Age	Sex	Degree of aortic stenosis	Heart wt.	Total coronary bore (sq. mm.)	Coronary atheroma*	Macroscopic fibrosis			
							M.I.	I.F.	L.F.F.S.	S.F.F.S.
8	40	M	Severe	865	70·7	I	1	+	2	14
9	48	F	Severe +A.I.†	763	52·5	I	0	++	4	11
10	61	M	Severe	699	68·0	I	1	+++	2	3
11	75	M	Moderate	290	38·9	I	0	0	0	13
12	56	M	Moderate +A.I.	790	68·0	III	1	+	2	2
13	78	M	Mild	497	60·7	V	1	++	3	3
14	65	F	Mild	499	45·1	0	0	0	0	0

* See text.
† Aortic incompetence.

M.I. = myocardial infarct.
I.F. = interstitial fibrosis.
L.F.F.S. = large focal fibrous scar.
S.F.F.S. = small focal fibrous scar.

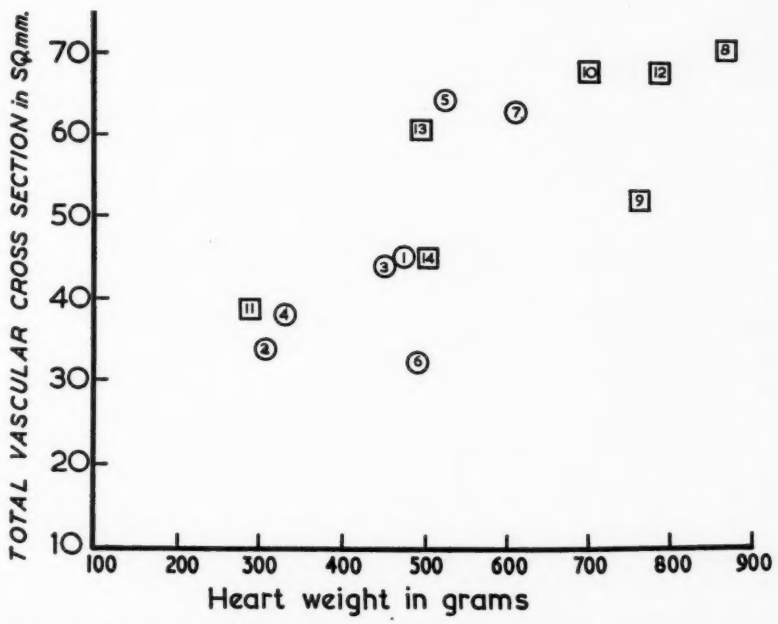

FIG. 1.—Graph illustrating the linear relationship between the heart weight and total cross-section of the main coronary vessels. Numbers 1 to 7 (in circles) are the cases of mitral stenosis; numbers 8 to 14 (in squares) are the cases of aortic stenosis.

The resulting graph (Fig. 1) showed a fairly close scatter along a straight line and indicates that there is a direct relationship between the size of the coronary arteries and the heart weight.

Myocardial Lesions. For the sake of clarity, macroscopic myocardial fibrosis has been described in arbitrarily chosen terms. The term old myocardial infarct refers to an area of solid fibrous tissue greater than 20 mm. in maximum dimension. Interstitial fibrosis refers to an area of streaky myocardial fibrosis of variable size. A focal fibrous scar refers to an area of solid fibrous tissue not greater than 20 mm. in maximum dimension. This type of lesion has been further divided into small focal fibrous scars (5 mm. or less in maximum dimension) and large focal fibrous scars (varying in size between 6 mm. and 20 mm. in maximum dimension).

Assessment of the degree of microscopic myocardial fibrosis was made on the blocks taken of muscle that appeared normal macroscopically. Here the term replacement fibrosis refers to areas of fibrous tissue replacing muscle cells. This is to be distinguished from the reticular fibrosis that is seen in chronic myocardial hypertrophy (Harrison and Wood, 1949). No attempt was made to distinguish rheumatic from ischæmic myocardial fibrosis.

Recent myocardial infarcts were not noted but areas of recent muscle necrosis were. These varied greatly in size, some being visible macroscopically, others only microscopically. They were characterized by necrosis and disappearance of muscle cells, preservation of the stroma, and some mononuclear cell infiltration. The end result was myocardial fibrosis due to fibrous tissue proliferation and/or stromal collapse (Fig. 5).

The descriptions below refer only to abnormalities seen in the left ventricular muscle since no significant changes were noted in the right ventricles.

Results

Mitral Stenosis. Four cases of mitral stenosis (Cases 1, 2, 3 and 4) and three cases of mitral stenosis and regurgitation (Cases 5, 6 and 7) were studied. There was no history of angina pectoris in any of the seven cases. The pathological findings are summarized in Table I. The myocardial infarct found in Case 1 could be accounted for on the basis of coronary artery disease. In Case 7, however, there was only Grade II atheroma of the left circumflex coronary artery and yet there was a large postero-basal myocardial infarct. There were no old myocardial infarcts in the other five cases. No areas of interstitial fibrosis or any large focal fibrous scars were noted in any of the seven cases. Five of the seven cases had small focal fibrous scars, the majority of these being situated in the posterior wall of the left ventricle. In Case 5 the three small focal fibrous scars were probably due to myocardial ischæmia resulting from an embolus described below. Of the remaining four cases with small focal scars, only in Case 4 (with the most severe degree of mitral stenosis) were these scars larger than 2 mm. in maximum dimension and in this case there were five scars measuring between 3 mm. and 5 mm. in maximum dimension. Also in Case 4, although there was no evidence of coronary atheroma, five recent mural thrombi (approximately 2–3 days old) were found in small coronary arteries (varying from 0·75 mm. to 2 mm. in diameter). None of these thrombi completely occluded a vessel but in areas of myocardium supplied by the affected vessels, microscopic areas of recent muscle necrosis measuring about 1 mm. in maximum dimension were found. Recent myocardial damage was not noted in the other six cases. Microscopic examination of normal appearing blocks of myocardium in all of the seven cases revealed at most only slight fibrosis.

Case 5 is of particular interest in that a piece of calcium was noted in the dissection to be lodged at the bifurcation of the right coronary artery posteriorly. Microscopic section of this (Fig. 2) showed an essentially normal vessel within which was a mass of calcareous material identical in appearance with the calcareous deposits on the mitral valve which had been split at operation one year before the patient's death. This mass in the lumen of the vessel is believed to be an embolus that originated from the mitral valve at the time of valvotomy or shortly thereafter. In the area of myocardium supplied by the right coronary artery there were three small focal fibrous scars. Mitral valvotomy had also been performed on Cases 2, 3, and 7; in Cases 2 and 3 the valves were not calcified and in Case 7 the valve was calcified but no coronary emboli were found.

FIG. 2.—Calcareous embolus lodged at the bifurcation of the right coronary artery in Case 5. Mitral valvotomy on a heavily calcified valve was performed one year prior to death and this embolus is believed to have originated from the valve at that time. It is firmly attached to the vessel wall by fibrous tissue. Barium gelatine injection fills the part of the lumen not occupied by the embolus. (×30).

Aortic Stenosis. The pathological findings in the seven cases of aortic stenosis studied are summarized in Table II. In Cases 9 and 14 calcific aortic stenosis was believed to have developed on congenital bicuspid aortic valves; in the remaining five cases the aortic stenosis was believed to be rheumatic in origin. The degree of stenosis of the aortic valve was graded mild, moderate, or severe according to whether the valve admitted the index finger, only the tip of the index finger, or less than the tip (Kumpe and Bean, 1948). Of the seven cases studied three had severe aortic stenosis, two moderate, and two mild. Cases 9 and 12 had significant aortic regurgitation in addition. Case 14 was the only one in which angina pectoris was noted, and this symptom disappeared with the correction of a severe anæmia. The three cases of severe aortic stenosis and Case 12 with moderate aortic stenosis had 18- to 24-month histories of congestive cardiac failure and grossly enlarged hearts.

The myocardial fibrosis in Case 13 (mild aortic stenosis) could be accounted for on the basis of severe coronary artery disease (Grades IV and V). In Case 12 (moderate aortic stenosis plus regurgitation) although there was Grade III atheroma of the right coronary artery and Grade II atheroma of the other major coronary vessels, the amount of myocardial fibrosis found was considered quite in excess of that to be expected from the degree of coronary artery disease present. The coronary lumina of the remaing five cases of aortic stenosis were normal (Cases 8, 9, 10 and 11 having Grade I atheroma and Case 14 had no coronary atheroma). Case 14 (mild aortic stenosis) had no macroscopic myocardial fibrosis, and Case 11 (moderate aortic stenosis) had thirteen small focal fibrous scars. Cases 8, 9 and 10 (severe aortic stenosis) had severe myocardial fibrosis, including old infarcts, interstitial fibrosis, and large and small focal fibrous scars. Microscopic examination of normal appearing blocks of muscle from these three cases revealed moderate to severe amounts of replacement fibrosis predominantly in the subendocardinal region of the left ventricle. There was reticular fibrosis throughout the left ventricle of each of these three cases.

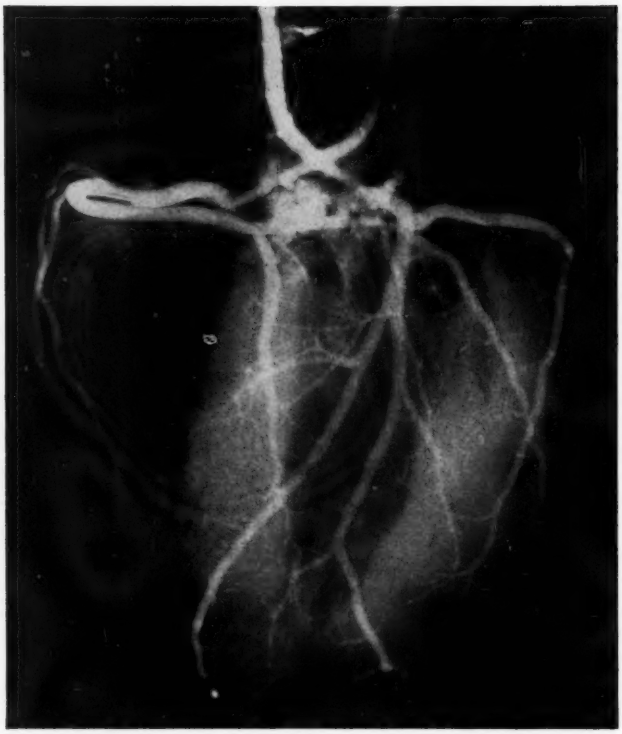

FIG. 3.—Aortic stenosis (Case 8), showing X-ray of injected heart. The vessels are enlarged and smooth bored in appearance. Note the heavily calcified aortic valve.

The radiograph of the injected heart in Case 8 is shown in Fig. 3. In spite of this seemingly adequate coronary arterial tree, in addition to the macroscopically visible myocardial fibrosis, there was an area in the outer quarter of the lateral wall measuring $2 \times 1 \times 1$ cm., throughout which confluent patches of recent muscle necrosis were seen (Fig. 4 and 5). Cases 9 and 10 showed microscopic areas of recent muscle necrosis in the subendocardial region of the left ventricle. In all the cases of aortic stenosis the various types of macroscopic fibrosis were greatest in the mid-portion of the left ventricular wall and least so in the subepicardial region. The postero-basal region of the left ventricle was the area most affected.

In the dissection of the coronary arteries of Case 9 a piece of calcium was noted to be lodged just proximal to the bifurcation of each of two small vessels (approximately 1·5 mm. in diameter). Microscopic examination of these pieces of calcium (Fig. 6) revealed that they were similar in appearance to the deposits on the aortic valve and it is believed that these are calcareous emboli that originated from this valve. In the microscopic examination of blocks of myocardium from this case a third calcareous embolus was noted to be lodged in the lumen of an arteriole. In Case 12 one such embolus was found just proximal to the bifurcation of an artery 2 mm. in diameter. It was not determined whether these emboli had caused any myocardial scarring or not. In none of the other cases of aortic stenosis were emboli found.

The results of necropsy in all patients with aortic and mitral stenosis at Hammersmith Hospital

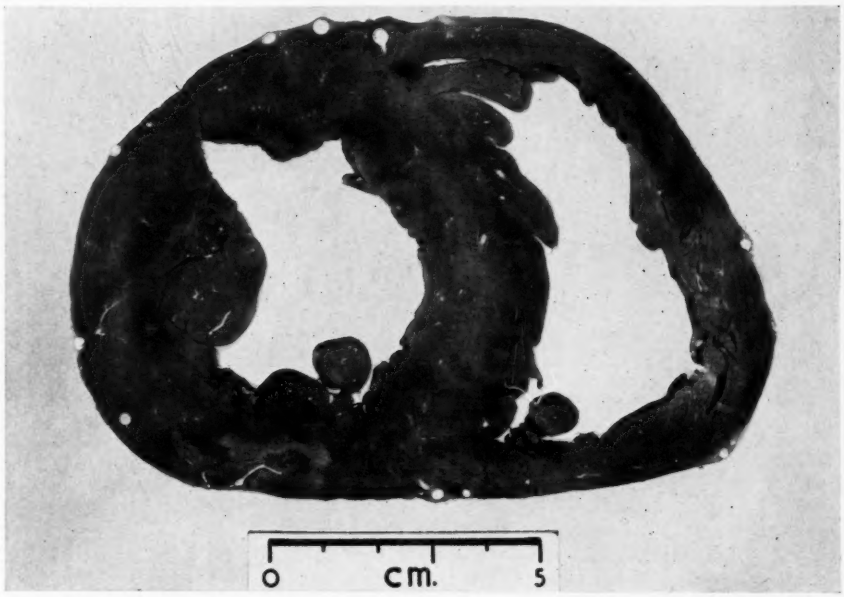

FIG. 4.—Aortic stenosis (Case 8), showing a slice of myocardium two-thirds of the way between apex and base. There is the scar of an old myocardial infarct in the posterior wall of the left ventricle, and in the outer one-quarter of the lateral wall are seen dark streaks of necrotic muscle. Note that the scar in the posterior wall does not involve the subendocardial region.

from 1948 to 1955 were reviewed for comparison with the present series. Of 88 cases of mitral stenosis only 4 had macroscopic myocardial fibrosis and reportedly normal coronary arteries. Two of these had old posterior myocardial infarcts and were subjected to special examination, while the other two cases had numerous foci of fibrosis in the posterior wall of the left ventricle. In one of the latter cases some of the foci of fibrosis were of recent origin. All four had severe mitral stenosis, overweight hearts, and long histories of congestive cardiac failure.

Of 63 cases of aortic stenosis 14 had macroscopic myocardial fibrosis and normal coronary arteries. The fibrosis in this group was described as being diffuse and patchy in seven cases, old postero-basal infarcts in two, a few fibrous flecks in two, patchy fibrosis in the postero-basal region in two, and a recent miliary infarct in one. Of these fourteen patients, seven had severe aortic stenosis, five had moderate aortic stenosis (one with aortic insufficiency), and two had mild aortic stenosis (one with aortic insufficiency). All had overweight hearts, only three weighing less than 500 g. Congestive cardiac failure had occurred in 13 of the 14 patients.

Although the necropsies of these hearts were necessarily less extensive, the findings agreed essentially with the present study. In aortic stenosis with normal coronary arteries, myocardial fibrosis occurred when the hearts were enlarged and the degree of stenosis was moderate or severe. Myocardial fibrosis was much less frequent in mitral stenosis with normal coronary arteries and in all of the four instances in which it occurred it was situated in the posterior wall of the left ventricle and the degree of mitral stenosis was severe.

DISCUSSION

Of the cases of mitral stenosis from the post-mortem series two had old posterior myocardial infarcts and one had numerous old and recent foci of fibrosis in the presence of normal coronary

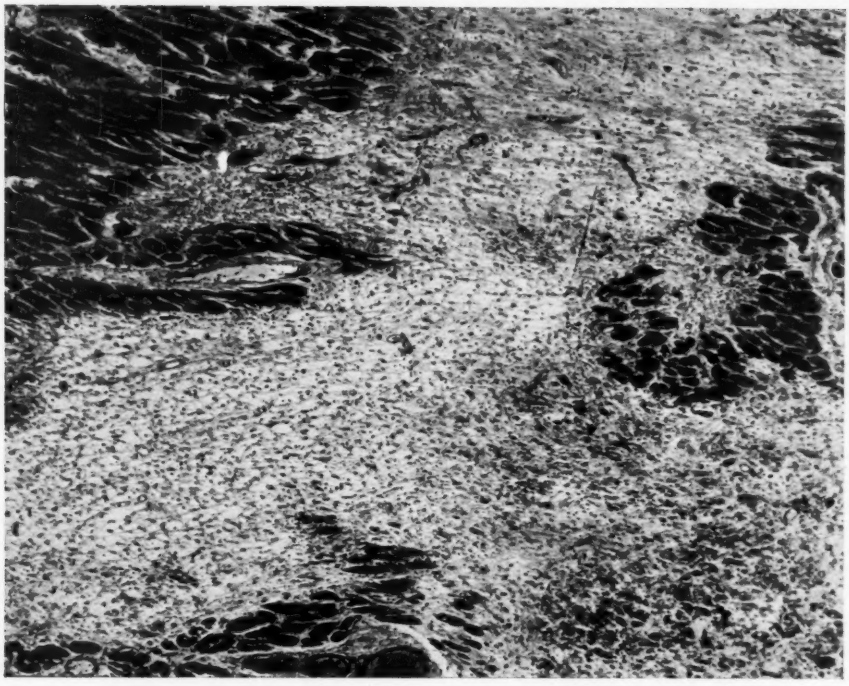

FIG. 5.—Aortic stenosis (Case 8), showing an area of recent ischæmic necrosis of muscle. In the lower right corner are seen necrotic muscle fibres, in the centre the necrotic fibres have disappeared leaving intact stroma, in the upper right corner fibrosis is occurring. Note injection mass in arteries. (×50).

arteries. These myocardial lesions could not be considered due to coronary artery disease, nor by their nature, could they be considered due to rheumatic myocarditis; nor could the myocardial infarct in Case 7 due to either of these causes. Of the hearts on the present series with small focal fibrous scars, only in Case 4 were these scars larger than 2 mm. in maximum dimension. In every instance there was either severe mitral stenosis or mitral stenosis plus regurgitation. Wood has drawn attention to the fact that angina pectoris in cases of mitral stenosis is more likely to occur when the degree of stenosis is severe or when there is in addition mitral regurgitation. He believes that the cardiac pain in these cases is due to myocardial ischæmia resulting from functional coronary insufficiency which in turn is related to a relatively fixed cardiac output. It is believed that the above-listed myocardial lesions are of the same causation. The lesions were almost entirely in the posterior wall of the left ventricle and Stuckey found that the electrocardiographic changes on exercise in the cases of mitral stenosis he studied, were greatest in the posterior leads (II, III and VF).

The small focal fibrous scars in Cases 2, 6, and 7 could also have been due to ischæmia or possibly to rheumatic myocarditis. Klinge (1930) found that "small white nodules" occurred in the myocardium of patients suffering recurrent attacks of rheumatic fever. He did not state the size of these nodules or how numerous they were, nor did he state whether they could occur following one attack of rheumatic fever. None of our seven cases were known to have had more than one attack of rheumatic fever. The aetiology of these small focal fibrous scars cannot be established

and Green and Gregg (1940) found a decreased systolic (and minute) coronary blood flow and

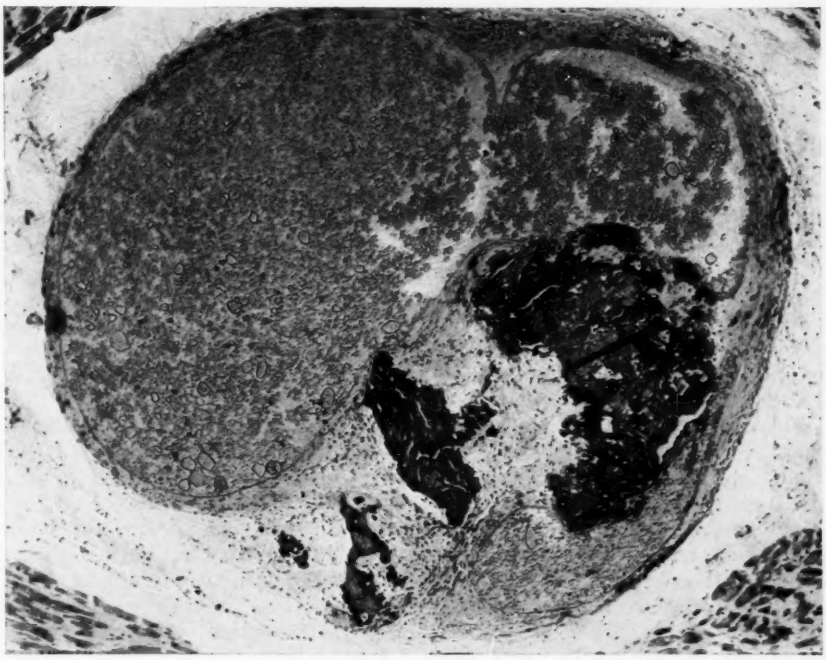

FIG. 6.—Aortic stenosis (Case 9), showing calcareous embolus lodged just proximal to the bifurcation of a small artery. There is destruction of the vessel wall in the lower portion of the photograph where the embolus is firmly attached by fibrous tissue. The rest of the vessel lumen is filled by barium.

with certainty, but it is evident from the seven cases of mitral stenosis that rheumatic myocarditis caused minimal, if any, macroscopically visible myocardial fibrosis.

Of the five cases of aortic stenosis with normal coronary lumina conspicuous myocardial fibrosis was found only in the three with severe aortic stenosis and grossly overweight hearts. This fibrosis could not be due to coronary artery disease, nor to rheumatic myocarditis since it was far in excess of the amount that may have been caused by this in cases with mitral stenosis. Similarly, since the size of the coronary arteries increased in proportion to the degree of cardiac enlargement, these areas of fibrosis cannot be considered due to myocardial ischæmia as a result of the myocardium outgrowing its blood supply. However, in hypertrophied, as in normal, hearts there is only one capillary per muscle fibre (Wearn, 1941). Since each muscle fibre is hypertrophied while each capillary remains of normal size (Payling Wright, 1954), enlarged hearts must be susceptible to ischæmia. There is no evidence that this factor alone causes myocardial fibrosis, at least not in hearts hypertrophied owing to hypertension (Harrison and Wood). By elimination, it is concluded that this fibrosis must be due to myocardial ischæmia as a result of functional coronary insufficiency. An area of recent muscle necrosis in the presence of normal coronary lumina in Case 8 supports this view. Friedberg and Horn (1939) have reported the occurrence of ischæmic muscle necrosis in the absence of coronary occlusion in cases of aortic stenosis, but all their patients had a significant degree of coronary artery disease.

Presumably, as with mitral stenosis, the fixed cardiac output in aortic stenosis plays a part in causing functional coronary insufficiency. The higher degree of myocardial fibrosis in the latter cases suggests that there must be additional factors. In experimental aortic stenosis, Green (1936)

and Green and Gregg (1940) found a decreased systolic (and minute) coronary blood flow and suggested that this was due to increased myocardial compression of the coronary vessels with resultant increased systolic peripheral coronary resistance in relation to the aortic systolic pressure. Also, Gorlin *et al.* (1955) have shown that the left ventricular stroke work in severe aortic stenosis was increased two to four times. Either or both of these factors, plus the left ventricular hypertrophy present, would render these patients more susceptible to myocardial ischæmia. However, the numerous areas of fibrosis in Case 11 with a heart of normal weight perhaps indicates that functional coronary insufficiency may exist in aortic stenosis in the absence of left ventricular hypertrophy. When aortic insufficiency is present in addition to aortic stenosis the degree of stenosis need not be so severe before a fixed cardiac output results (Gorlin *et al.*). This perhaps explains why in Case 12 much myocardial fibrosis was present in spite of only moderate aortic stenosis and relatively mild coronary artery disease.

The areas of ischæmic necrosis in the eight cases of aortic stenosis reported by Friedberg and Horn were mainly situated in the subendocardial region of the anterior wall of the left ventricle. The myocardial fibrosis in congenital aortic stenosis reported by Marquis and Long was also in the subendocardial region of the left ventricle. In the present study of aortic stenosis the fibrosis was greatest in the deep parts of the left ventricular wall and mainly posteriorly. Possibly these fibrous scars represent infarcts of muscle bundles. In aortic stenosis tremendous strain falls upon the deep bulbo-spiral muscle bundle which would thus be more susceptible to myocardial ischæmia.

The finding of Kumpe and Bean (1948), and Lewes (1951), that cardiac pain was an index of the severity of the aortic stenosis, agrees with this study in that, although no case suffered from angina (except Case 14 when severely anæmic), the degree of myocardial fibrosis was roughly proportional to the degree of valvular stenosis. The degree of myocardial fibrosis in aortic stenosis was far in excess of that found in mitral stenosis. This is in agreement with the incidence of angina pectoris in the two groups. Wood noted anginal pain in 8 per cent of cases of mitral stenosis, whereas in aortic stenosis Kumpe and Bean noted it in 37 per cent, and Horan and Barnes (1948) in 28 per cent.

Although congestive cardiac failure might accentuate the functional coronary insufficiency in either mitral or aortic stenosis, it is not considered to be an essential cause of the ischæmic myocardial lesions in either group.

Cases 9 and 12 are of considerable interest because of the calcareous emboli that were shed from the aortic valves into the coronary arteries. In heavily calcified valves the most superficial portion of the calcareous material is sometimes seen to be rather loosely attached and friable either in the sinuses of Valsalva or on the ventricular surface of the valve. Perhaps the most obvious way for calcareous coronary emboli to arise from a diseased aortic valve would be for them to be swept into the coronary arteries from the calcium in the sinuses of Valsalva during diastole. However, in Cases 9 and 12 examination revealed only well attached calcareous material in this area. On the ventricular surfaces of the valves, however, there were masses of calcium of which the most superficial portions were loosely attached; it is believed that the calcareous fragments were broken off from the undersurface of the valves during systole, when this area would have been subjected to a high intraventricular pressure and increased rate of blood flow past the stenosed orifices. During diastole, especially when aortic regurgitation is also present, as it was in each instance, the emboli could be carried back in the regurgitant flow into the coronary orifices. That such emboli could cause myocardial ischæmia seems evident, but whether their number or size is significant is as yet undetermined.

Of further interest is the calcareous embolus to the right coronary artery in Case 5 following valvotomy on a heavily calcified mitral valve. In reviewing the data at necropsy, one other instance was found where a piece of calcium had lodged in the coronary artery following valvotomy on a calcified mitral valve. Although in neither patient did the embolus have any significant effect on the myocardium supplied by the vessel in which it lodged, it is possible that myocardial infarction could be a consequence.

Knowing that calcareous emboli can occur from a calcified aortic valve spontaneously and from a calcified mitral valve following valvotomy, the probability that they occur following aortic valvotomy seems evident. One would expect them to be numerous following aortic valvotomy because this valve is usually heavily calcified; also one would expect coronary emboli to be especially frequent because of the proximity of this valve to the coronary orifices.

Summary and Conclusions

A coronary artery injection technique combined with a careful examination of the myocardium was used to study the hearts of seven cases of aortic stenosis and seven cases of mitral stenosis. An attempt was made to assess the amount of myocardial fibrosis that could not be considered due to coronary artery disease or to rheumatic myocarditis but therefore presumably due to functional coronary insufficiency. In addition the findings at necropsy in 88 patients with mitral stenosis and 63 with aortic stenosis were reviewed.

In aortic stenosis the amount of myocardial fibrosis occurring as a result of functional coronary insufficiency is related to the degree of stenosis of the aortic valve and the degree of left ventricular hypertrophy. When both of these are severe the fibrosis may be extensive.

Myocardial fibrosis as a result of functional coronary insufficiency may also develop in severe mitral stenosis, or in mitral stenosis and insufficiency, but it is much less common and much less extensive than in aortic stenosis. The fibrosis associated with mitral disease was almost entirely in the posterior wall of the left ventricle.

There was no evidence to suggest that rheumatic myocarditis causes any significant degree of macroscopically visible myocardial fibrosis.

Calcareous emboli may arise spontaneously from a heavily calcified aortic valve, and also from a heavily calcified mitral valve following valvotomy. Attention is drawn to the probability that such emboli would occur following aortic valvotomy.

I am very grateful to Professor C. V. Harrison, at whose suggestion this study was undertaken, for his advice, criticism, and encouragement. To him and to Dr. I. Doniach I am indebted for their help in the preparation of this paper. My thanks are also due to Dr. S. Daftary for the radiographs, to Mr. J. Griffin and the histology staff of the Postgraduate Medical School, to Miss R. Klein for the photographs, and to Mr. F. G. Saunders for Fig. 1.

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ANEURYSM OF THE MITRAL VALVE IN SUBACUTE BACTERIAL ENDOCARDITIS

BY

NEIL MACLEAN AND MARY K. MACDONALD

From the Department of Pathology, University of Edinburgh

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The commonest form of cardiac valvular aneurysm is the thrombo-aneurysm of Ribbert (1924), which arises by perforation of an ulcer of the valve cusp into a hollow thrombotic mass and by organization undergoes fibrosis of varying degree. Reports of such aneurysms are not infrequent in the early reports of bacterial endocarditis, but aneurysms having well-organized, smooth, fibrous walls are rare; Saphir and Leroy (1945) believe that some of them are true aneurysms resulting from the action of intra-ventricular pressure upon a portion of valve cusp weakened by valvulitis. The aneurysms affect the aortic valve more commonly than the mitral (Pelvet, 1867; Osler, 1908; Horder, 1909; von Arx, 1914; Soulié and Porge, 1937), and involve the anterior (aortic or right) cusp of the mitral valve much more often than the posterior. Habershon in 1855 described a smooth-walled aneurysm, 1·9 cm. in diameter, affecting the aortic cusp of the mitral valve, and Ogle (1858 *a* and *b*) described two smaller examples. Of the 23 cardiac valvular aneurysms collected by Pelvet, 9 affected the mitral valve. More recent instances of mitral valvular aneurysms are those of Horder (1909, Fig. 14), Calwell (1912), von Arx (1914), Whimster (1928), Pichon and Bidou (1932), Soulié and Porge (1937), Soulié *et al.* (1947), Saphir and Leroy (1948), Libman and Friedberg (1948), and Musallam and McCall (1953).

In this paper we report an extreme example of aneurysmal deformity of the mitral valve in a patient who survived for five years after an attack of subacute bacterial endocarditis treated with penicillin, and a further case that illustrates some aspects of the pathogenesis of the lesion.

Case Reports

Case 1. This man was well until he developed subacute bacterial endocarditis at the age of 44. Streptococcus viridans was isolated from his blood and he received 41 mega units of penicillin in the course of six weeks. At the time of admission to hospital, aortic incompetence was the dominant cardiac lesion, and although mitral murmurs were heard during his illness, the radiological appearances remained those of predominant aortic incompetence. He was discharged from hospital seven months later, and from this time onwards he was breathless on mild exertion; at the age of 46, he began to have congestive cardiac failure. When he was admitted for the last time, aged 49, in gross failure, there was predominant mitral incompetence, moderate aortic incompetence, and some mitral stenosis.

Autopsy Findings. All organs showed evidence of advanced congestive heart failure, and there was a large recent infarct in the middle lobe of the right lung.

The heart weighed 770 g. A large, slug-like thrombus was present on the postero-lateral wall of the right atrium. Both ventricles and the left atrium were dilated and hypertrophied. No recent vegetations were present on any part of the mural or valvular endocardium. The aortic valve was incompetent and possessed only two cusps, a posterior or non-coronary cusp and an anterior cusp in which a raphe of congenital type (Lewis and Grant, 1923; Koletsky, 1941) represented a rudimentary commissure between right and left coronary cusps. Both aortic cusps were large and thickened by fibrosis, but showed no nodularity. The mitral ring was dilated, admitting four fingers. The posterior cusp of the mitral valve appeared normal, but the anterior cusp was thickened by fibrosis which extended into the chordæ tendineæ of the anterior papillary muscle. From the anterior cusp an aneurysm, 4 cm. in depth, projected through the mitral ring, into the left atrium (Fig. 1). The smooth wall of the sac was composed of fibrous tissue: three perforations,

FIG. 1.—Case 1. Left atrium seen from above. Two perforations are seen in the wall of the aneurysm, which projects into the atrium.

FIG. 2.—Case 1. A portion of the left ventricle, showing the orifice of the aneurysm of the anterior cusp of the mitral valve, and the patch of endocardial fibrosis on the upper part of the interventricular septum.

each 6 mm. in diameter, were present, two in the dome of the aneurysm, and another in the posterior wall near its attachment to the valve cusp. The sac contained no thrombus. The orifice of the aneurysm (Fig. 2) measured 25 mm. and 17 mm. in transverse and antero-posterior diameters respectively, and its margins were thick and bordered by small calcified nodules, resembling healed vegetations. A patch of fibrous thickening, 12 mm. by 4 mm., was present on the endocardial surface of the upper posterior part of the interventricular septum, on its left ventricular aspect.

Case 2. The patient was discovered at the age of ten years to have pulmonary and mitral systolic murmurs, and a presystolic triple rhythm at the apex. He had no apparent cardiac disability, and no rheumatic history. For five years he continued to feel well: six weeks before death he complained of pain in the left loin. Subsequently he became breathless on exertion, and developed a cough. Just before admission he had attacks of vomiting and diarrhœa, with abdominal pain, and one small hæmoptysis.

On admission to hospital he was found to have a pulse rate of 160 a minute, a respiration rate of 48 a minute, and a normal temperature. He was tender in the right iliac fossa; no abnormality was found clinically in the heart and lungs, but radiological examination showed some cardiac enlargement and pulmonary œdema. He was thought to be suffering from a virus infection, and intravenous terramycin therapy was started, but he died suddenly a few hours later.

Autopsy Findings. The heart was dilated, and both ventricles showed hypertrophy. The tricuspid and pulmonary valves showed no significant abnormality but the aortic valve was bicuspid and slightly stenotic and incompetent. The posterior and the right coronary cusps were united, and there was a low median raphe on the floor of the cusp. The two aortic cusps, which will be referred to as the conjoined and left coronary cusps, were of similar size; their anterior portions were thickened by fibrosis and had slightly patulous and everted margins. A perforation 15×5 mm. was present in the conjoined cusp. Both aspects of the cusps were covered with small organizing but still partly friable vegetations, which were continuous with similar vegetations on the ventricular aspect of the base of the anterior cusp of the mitral valve. There they surrounded an orifice, 5 mm. in diameter (Fig. 3): this opened into an aneurysm which measured 13 mm. in diameter and projected into the left atrium (Fig. 4). The outer surface of the aneurysm was smooth except at the apex where a perforation, 5 mm. in diameter, was encircled by partially organized vegetations. No abnormality was seen in the posterior cusp of the valve.

FIG. 3.—Case 2. Left ventricle. Much of the left coronary cusp has been removed to display the orifice of the aneurysm of the anterior cusp of the mitral valve. The perforation of the conjoined cusp is hidden.

FIG. 4.—Case 2. Left atrium and mitral orifice seen from above. The aneurysm at the base of the anterior cusp of the mitral valve projects into the atrium.

The other organs were congested: the spleen was enlarged to approximately twice normal size, and contained a pale infarct.

DISCUSSION

Good descriptions of the gross appearances of the larger aneurysms of the mitral valve have been given by Rokitansky (1852) and more recently by Soulié and Porge (1937). The aneurysms are commonly situated near the base of the anterior cusp and project into the left atrium, but they may be situated nearer the free margin of the cusp and project into the ventricle. They measure up to 4 cm. in diameter (Case 1), are commonly saccular, and have a wide orifice: the largest aneurysms show most organization. The sac may contain blood clot or thrombus.

Soulié and Porge believe that the aneurysms result from disease affecting primarily the aortic valve: they stress the almost invariable integrity of the posterior cusp of the mitral valve as indicating that former rheumatic endocarditis of the mitral valve plays little part in their pathogenesis. In their opinion, the elective localization of the aneurysms of the mitral valve is due to direct spread (" marche descendante ") of bacterial endocarditis from the aortic valve to the ventricular aspect of the anterior cusp of the mitral valve. With this conclusion we are in broad agreement, although, of course, neither the aneurysms that are not associated with bacterial endocarditis (Musallam and McCall), nor those affecting the posterior mitral cusp can be explained in this way.

Localization of the bacterial infection might, however, be due also to impingement of a regurgitant stream from an incompetent aortic valve on the ventricular or valvular endocardium. Such a regurgitant stream in cases of uncomplicated aortic incompetence frequently causes localized thickening and pockets in the subaortic endocardium, which may become involved in bacterial endocarditis. In similar circumstances thickening may develop on the ventricular aspect of the

anterior cusp of the mitral valve (Edwards *et al.*, 1948). The incidence of aortic incompetence in cases of mitral valvular aneurysms is high, as is exemplified by the cases of von Arx, Soulié *et al.*, Coulson (1850), Peacock (1851), Habershon, Calwell, Whimster, and Soulié and Porge. In this connection, cases of aortic incompetence in which the anterior mitral cusp was the sole site of bacterial vegetations are of particular interest: such are the cases described by Peacock, Calwell, and Horder (1906). In the museum of the Pathology Department of the University of Edinburgh there is a specimen (MB.2640) of pneumococcal endocarditis in a woman, aged 30, with a past history of rheumatic fever and clinical evidence of mitral stenosis: the mitral and aortic valves show post-rheumatic fibrosis but only minute verrucous vegetations are present on the aortic and posterior mitral cusps. The ventricular aspect of the anterior cusp of the mitral valve, however, is extensively ulcerated and at a corresponding site on the opposite side of the cusp a polypoid thrombotic vegetation projects into the left atrium for a distance of 2 cm.

In both of the cases reported here, the aortic valves were bicuspid. Such valves tend to become thickened and sclerosed (Paget, 1844; Koletsky) and as a result may become stenotic and incompetent (Smith and Matthews, 1955); also related, in all probability, to this tendency is their well-known susceptibility to bacterial endocarditis. Our cases illustrate both points. In Case 1, aortic incompetence and left ventricular enlargement were well-established when the patient first came under observation with subacute bacterial endocarditis. In Case 2, cardiac murmurs were present five years before death, and the hypertrophy of the left ventricle indicated an aortic lesion of some duration.

Well organized aneurysms of substantial size can develop in the course of subacute bacterial endocarditis only if the disease is sufficiently prolonged to allow healing to accompany the ulcerative process. In untreated cases they are therefore more likely to be met with in the bacteria-free stage as mentioned by Libman and Friedberg than in an actively progressive phase of the disease. In patients treated with penicillin an increased incidence of aneurysms might be expected where valvular destruction was advanced before the therapy was instituted or where control of the disease was incomplete. Such was the experience of Saphir and Leroy, who attributed the high incidence of aneurysms in their later cases to penicillin therapy. It is apparent that this and other valvular distortions can be avoided only by early diagnosis. That adequate therapy alone may not be enough is demonstrated in Case 1 where the patient developed the largest aneurysm of the mitral valve yet recorded after surviving an attack of subacute bacterial endocarditis for five years.

Summary

Two cases of aneurysm of the mitral valve are reported. One occurred in a patient with active, untreated subacute bacterial endocarditis. The other, the largest yet recorded, occurred in a patient who died in congestive cardiac failure five years after an attack of this disease treated by penicillin. In both instances the aortic valves were bicuspid.

The nature and pathogenesis of such aneurysms is discussed, and the importance of previous aortic valvular disease in these patients is stressed.

We are grateful to Professor G. L. Montgomery for helpful criticism, to Dr. R. M. Marquis for the history of Case 1, and to Dr. A. W. Wright and Mr. N. A. Gray for the clinical details of Case 2. The illustrations are the work of the Photomicrography Unit of the University of Edinburgh.

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LIFE EXPECTATION OF PATIENTS WITH MITRAL STENOSIS WITH AND WITHOUT OPERATION*

BY

E. DONZELOT, R. HEIM DE BALSAC, P. SAMUEL, AND E. BEYDA

From the Clinique Cardiologique de Faculté de Medicine de Paris (Hôpital Broussais-La Charité)

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Many recent publications have dealt with the physiopathology and hæmodynamics of mitral stenosis, the diagnosis of mitral regurgitation, and the surgical treatment of the mitral stenosis. Only a few workers—Vedoya *et al.* (1954), Ellis and Harken (1955), and Olessen (1955)—have studied what happened later on to patients with mitral stenosis who did not undergo valvotomy for one reason or another. This problem is, however, of interest especially if it is possible to compare the life expectation of these patients with that of the patients who have had operations.

Material. Our first mitral valvotomies go back to February, 1951. Since then we discussed systematically the opportunity of an operation for each patient with mitral stenosis. Up to September 1954, 165 patients have been operated on and most of them regularly followed up since. During the same period, 200 other patients have been examined: 43 have not been re-examined and 157 have been up to May, 1956. Our material includes therefore 322 patients who have been followed up over a period of 20 months to 5 years (Table I).

TABLE I

PROGRESS OF PATIENTS AFTER VALVOTOMY AND OF PATIENTS WHO HAVE NOT HAD VALVOTOMY

Group	Number of patients examined	Condition of the patients followed-up over a period of 20 months to 5 years			
		Dead	Worse	No change	Improved
Group 1—Non-operable (major and final contra-indication)	120	59	39	22	0
Group 2—No operation (temporary contra-indication) ..	7	0	1	3	3 (operated)
Group 3—No operation (mitral stenosis only slight)	11	1	1	9	0
Group 4—Operable but no operation ..	19	11 (58%)	4 (21%)	4 (21%)	0
	157				
Operated	165	16 (9·7%)	2 (1·2%)	14 (8·5%)	133 (80·6%)

RESULTS

We classified the 157 patients who did not have operations in the following groups.

Group 1: Major and final contra-indications to operation

This group includes 120 patients with a severe valve lesion or pulmonary hypertension accompanying their mitral stenosis or with irreversible heart failure and a very large heart—all conditions that constitute a major and final contra-indication to valvotomy.

* Communication given to the 18th Congress of the Italian Society of Cardiology at Trieste, May, 1956.

At the time of their examination, 29 patients were in sinus rhythm while 91 others were in auricular fibrillation. A loud rough apical systolic murmur propagated towards the axilla and imputed to mitral incompetence was noted in 113 patients. An important lesion of the aortic orifice (incompetence or stenosis or both together) was reported in 65 cases and a tricuspid lesion was diagnosed in 15 when there was expansile pulsation in the liver. Pulmonary incompetence, probably functional from dilatation of the pulmonary ring and pulmonary hypertension, was suspected once only. Pulmonary arteritis was suspected in one other. Two patients showed noticeable arterial hypertension. Ninety-four patients had heart failure, left, right, or general, more or less evident or absolutely irreversible with an enlarged heart.

This group is obviously heterogeneous because it includes aged adults with advanced myocardial degeneration and young patients with several valvular lesions but with a cardiac compensation that allows them to live normally or nearly so. Furthermore, the distribution of the various orificial or myocardial lesions we took account of is not the same, two or more of them often being present in the same patient. For example, mitral incompetence was recorded in 113 of the 120 with mitral stenosis and in 94 of those with cardiac failure. The common point of all these patients is having mitral stenosis associated with another severe lesion that constitutes a straightforward and final contra-indication to a mitral valvotomy.

Of these, 59 (49%) died: 45 of cardiac failure, 3 of pulmonary thrombosis, 2 of verified cardiac thrombosis, 3 of hemiplegia, and 6 of pulmonary embolism. Sixty-one (51%) are still alive: 39 (33%) have a severe cardiac failure that prevents them from working or even from doing anything, and 22 (18%) have been either well compensated or only slightly decompensated and able to carry on some slight activity.

These various figures are in substantial agreement—the 26 patients with cardiac failure corresponding to the 22 who are alive with but slight disability and the 94 with cardiac failure corresponding to the 59 dead and to the 39 still alive but in a precarious condition.

The very high death rate (49%) in this group of patients followed for from 2 to 5 years and the unsatisfactory condition of survivors (33%) emphasize both the gravity of the mitral failure and the cogency of our operatory contra-indications for these categories of patients with severe lesions. Our figures are in agreement with Vedoya *et al.* (1954) who in similar conditions (one to three years) record a mortality of 27 to 66 per cent and with Olessen (1955) who reports a death rate of 70 per cent in twelve years, among the patients with mitral stenosis followed up by him.

Group 2: Temporary contra-indications to operation (7 cases)

Seven only of our patients showed a temporary contra-indication, that is their cardiac condition demanded valvotomy but another cause demanded that this should be deferred. Renal tuberculosis, pulmonary tuberculosis, subacute bacterial endocarditis, and in four cases a bout of acute rheumatism were the various causes in our cases.

Three of these patients have had successful valvotomy since and three others will soon undergo the operation. The seventh, a 12-years-old child, is still afflicted by a rheumatic process which is making his lesion worse and will probably leave him in the first non-operable group.

Group 3: No indication for operation as the mitral stenosis is not severe (11 cases)

Mitral stenosis that is not severe (mitral area estimated at more than 2 cm.) does not need operation because of the small disability resulting and the limited correction that can be brought by surgery with small profit for the patient.

Eleven of our patients were included in this group. All are women; seven under 35 years, one 40, and three about 60. Almost all have a pure mitral stenosis that is relatively well tolerated with little repercussion on the pulmonary circulation and the right side of the heart.

When followed up, five still live normally and four have as yet only minor disability. But one has had acute pulmonary œdema and is in heart failure, and another has died probably from pulmonary embolism.

Patients of this group must therefore be observed regularly every six months. Their condition may change and a complication may occur. A real danger threatens them and an operation may be able to save most of them. Consequently a time will come when valvotomy cannot be delayed any longer. We do not want to say that an operation will be needed by every patient with mitral stenosis. Indeed, three of the eleven patients in this category (3 of 322 of our material) reached sixty years of age with a recognized mitral stenosis that had existed probably for many years. They represent the small group of non-evolutive mitral stenosis where up to an advanced age the valvular lesion is tolerated without progressive development and without creating hæmodynamic trouble. The percentage among our material (1%) is lower than the reality because many patients without symptoms do not ask for a periodical examination.

Group 4: Positive indication for operation which was delayed or refused (19 cases)

This is the most instructive group for it includes all the 19 patients with a mitral stenosis who have not had valvotomy although there were positive indications for it. 12 refused the operation which was proposed to them; 6 accepted it but preferred to defer it to a time more convenient for them. The last with mitral stenosis severe enough to produce pulmonary œdema died before his operation was arranged.

Of these 19 patients, 11 (58%) died in less than 5 years—5 of acute pulmonary œdema, 2 of pulmonary embolism, 1 of hemiplegia, and 3 of heart failure. 4 (21%) are in a bad condition too advanced for operation, and 4 only (2½%) are in a condition comparable with that at the time of their first examination. These figures are very close to those obtained by Ellis and Harken (1955): they recorded the following year 17 deaths among the 19 patients with mitral stenosis who refused the operation.

Discussion

The above facts emphasize the gravity of mitral stenosis. They reflect a general opinion that can be checked by all heart specialists when recollecting how many patients with mitral stenosis they have kept under observation for the past ten years.

However, they lead to another remark: the patients of this category have been deemed operable as well as the 165 who had operations. The same criteria were used, and age, sex, and clinical conditions were the same. We are thus entitled to compare the life expectation of the patients in Group 4 with those who had operations.

Among these (165 cases) we record 10 (6%) deaths at or soon after operation and 6 (3·6%) deaths later—a total of 16 (9·7%) of the 165 operated and followed up from 2 to 5 years. 16 others (9·7%) did not get any benefit from the operation, 13 of them having been probed only. 133 (80%) were improved so much that more than 100 work again and have a normal and comfortable life.

The results are compared in Table I and this comparison hardly needs any comment. It is striking to oppose the two categories of those who had and those who had not an operation. We must add this material includes the first cases operated by the surgical team of Broussais Hospital, i.e. at a time when we had had little experience, and the recent results are better. Since September, 1954, one of us with Dubost carried out valvotomy for a hundred patients with mitral stenosis without any recorded death, either at or just after operation.

Our figures show clearly the extreme gravity of the evolution of mitral stenosis when the stage of severe symptoms has been reached, for half of them die within 5 years and the majority within 10 years after this stage has been reached. Further, the improvement of these conditions after valvotomy must be noted. After some years of experience, the operation appears to be of great value.

Conclusion

From our statistical study which covers 322 patients with mitral stenosis (165 with and 157 without operations) followed up from 2 to 5 years, these features should be emphasized.

(1) The gravity of the evolution of mitral stenosis, whether this is pure or associated with congestive failure or with another lesion.
(2) The satisfactory results from mitral valvotomy: 133 of 165 operated, (80%) were improved so much that they were able to work again or enjoy a reasonable life.
(3) The decisive comparison of life expectation for two similar series, one with and one without operations, emphasizes the great value of valvotomy.

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HAEMODYNAMIC EFFECTS OF SQUATTING DURING REPOSE*

BY

LEON BROTMACHER

From the Cardiac Department, Guy's Hospital

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The tendency of children with cyanotic congenital heart disease to squat when tired or breathless was described by Taussig in 1947, but the reasons for the adoption of this striking posture have been surprisingly little studied. Lurie (1953) found that inflating cuffs on the thighs obviates the need to squat and suggested that venous reservoirs in the legs are compressed and brought nearer to heart level by squatting: the effects of gravity, which causes pooling of blood in the legs and a fall in cardiac output with standing, are thereby countered. Callebaut *et al.* (1949), on the basis of oximetric studies, suggested that squatting increases systemic resistance and reduces the veno-arterial shunt. With these exceptions, virtually no investigations into the hæmodynamic effect of squatting have been made in cyanotic patients.

The present investigation was made to try to explain the tendency of severely incapacitated patients with cyanotic congenital heart disease to lie continuously in a squatting position, even when they have not been exercising. The effects of squatting in an upright position during recovery from exercise are considered in a separate communication (Brotmacher, 1957*b*). Patients with acyanotic congenital heart disease and subjects with normal hearts have also been studied in an attempt to determine whether the changes observed are peculiar to squatters or are general ones that benefit patients with a veno-arterial shunt as a result of their cardiac abnormality.

Material and Methods

Measurements of the effect of squatting on systemic and pulmonary blood flow were made on 13 squatters and 17 control subjects.†

In order to obtain the maximum possible co-operation from patients who were not being anæsthetized, they were shown the room in which the procedure was to be carried out, and this was explained in an appropriate manner. Sodium amytal was given an hour before starting. All examinations were performed in the morning, the patients having fasted since the previous evening, apart from a cup of tea at least two hours before. Anæsthesia, when used, was induced by thiopentone sodium given intravenously or injected down the catheter. The patients had invariably been in position for at least half an hour before the control observations were made. The position usually adopted by the squatters when recumbent was then reproduced as far as possible. The legs were passively flexed, slightly abducted and laterally rotated at the hips, and flexed at the knees, the thighs being brought as near as possible to the flanks. The legs were supported in this position so that no exertion was required of the patients.

Blood samples were obtained after the patient had been in position about one minute, and at least five minutes were allowed to elapse between lowering the legs and obtaining control blood samples at other sites. The oxygen consumption was measured over periods of two to four minutes with the patient breathing air, a modification of the Benedict spirometer (Christie and Donald, 1949) being used. The blood oxygen content was measured by the Haldane method (Douglas and Priestley, 1948) and oxygen capacity calculated from the hæmoglobin percentage, which was determined by photo-electric colorimetry.

* Work forming part of a thesis accepted for the degree of Ph.D. by the University of London.

† Further particulars relating to these patients are contained in an appendix that is available on request.

The values obtained were used to calculate the blood flows by application of the Fick principle. The criteria for recognition of an arterio-venous shunt were those described by Holling and Zak (1950), and an arterial oxygen of less than 94 per cent was regarded as indicative of a veno-arterial shunt. When necessary, pulmonary venous blood was assumed to have an oxygen saturation of 96 per cent.

A number of observations were made in patients being anæsthetized for angiocardiography. Rectal thiopentone sodium was used for premedication and anæsthesia maintained with cyclopropane, the depth required being somewhat greater than that needed for cardiac catheterization. Observations were made with the patient breathing pure oxygen, and full saturation of pulmonary venous blood assumed. Oxygen consumption was measured with a Benedict spirometer, using oxygen, and a sample of mixed venous blood obtained at the same time, a cardiac catheter having previously been advanced as far as the right atrium. The catheter was then withdrawn and the investigation continued in the usual way. As an inhalation anæsthetic was employed, the Haldane method of blood gas analysis could not be used. The oxygen contents and capacities were therefore estimated with the Beckman spectrophotometer.

Pressures were measured with Southern Instruments capacitance electromanometers connected to a Brush oscillograph. In all but one patient, in whom the aorta was intubated through a persistent ductus arteriosus, systemic pressures were recorded in the brachial artery, which was punctured with a 21-gauge needle connected to the electromanometer by plastic tubing of 2 mm. internal bore. All pressures were measured from midway between the sternal angle and the tip of the fourth thoracic spinous process.

In the absence of a veno-arterial shunt, the arterial oxygen content remains remarkably constant. Observations in four control subjects (Table I) showed that it was not altered appreciably by squatting, and in the

TABLE I

EFFECT OF SQUATTING ON ARTERIAL OXYGEN

A. Samples obtained during cardiac catheterization

Case No.	Arterial O_2 content (ml./100 ml.) Controls			Case No.	Arterial O_2 content (ml./100 ml.) Squatters		
	Supine	Squatting	Difference		Supine	Squatting	Difference
10	14·0	13·9	−0·1	21	24·6	24·3	−0·3
12	15·7	15·5	−0·2	22	23·6	23·5	−0·1
,31	17·5	17·4	−0·1	23	15·3	15·4	+0·1
32	19·3	19·2	−0·1	24	16·3	16·8	+0·5
				33	27·8	28·0	+0·2

B. Oximetric observations on squatters

Case No.	Percentage saturation of arterial blood		
	Supine	Squatting	Supine
22	89	88	89
23	95	95	95
27	87	87	87
34	97	97	97
35	94	92	94

remaining acyanotic patients it was assumed to be the same when squatting as when supine. This assumption was also made in four squatters: it has been shown by volumetric analysis and by ear oximetry (Table I) that squatting does not alter the oxygen saturation of these patients appreciably. In four subjects an arterial sample was not obtained. There was no history of cyanosis and no hæmodynamic basis for a veno-arterial shunt; their systemic and pulmonary flows were calculated on an assumed 96 per cent saturation of pulmonary venous and systemic arterial blood. In one patient with, *inter alia*, an atrial septal defect, no inferior vena caval sample was obtained while squatting. The superior vena caval oxygen content remained unchanged and that of pulmonary arterial and right atrial blood changed by only 0·1 and 0·2 ml./100 ml. respectively. Flows when squatting were calculated on a presumed absence of alteration in the saturation of mixed venous blood.

RESULTS

Fourteen observations of the effect of squatting on systemic blood flow were made in control subjects (Table II). In all but two the flow was higher when squatting than when supine. There

was no change in systemic blood flow in one of the exceptions and a two per cent fall in the second, who was thought to have primary pulmonary hypertension and gave a history of syncopal attacks on exertion and may well have had a fixed cardiac output. The mean increase for the entire group was 42 per cent and the maximum 108 per cent.

There was a tendency for the arterio-venous oxygen difference to lessen (Table II), but the changes were small in extent and not consistent. The mean decrease was less than 0·4 ml./100 ml. The increase in systemic blood flow was associated for the most part with a rise in oxygen consumption, which was observed in all but two subjects (Table II). The changes in these two parameters do not bear a very close relationship, but the subjects who had a large increase of systemic flow had also a large increase of oxygen consumption. There was no relationship between the initial levels of the oxygen consumption and the arterio-venous oxygen difference on the one hand, and the changes produced by squatting on the other.

TABLE II

EFFECT OF SQUATTING ON OXYGEN CONSUMPTION, ARTERIO-VENOUS DIFFERENCE AND SYSTEMIC BLOOD FLOW. CONTROL SUBJECTS

Case No.	Oxygen consumption (ml./min.)		*a*−*v* difference (ml./100 ml.)		Systemic flow (l./min.)	
	Supine	Squatting	Supine	Squatting	Supine	Squatting
1	192	176	6·0	4·5	3·2	3·9
2	213	231	6·0	4·7	3·5	4·9
3	158	160	—	—	—	—
4	208	237	7·4	7·0	2·8	3·0
5	129	149	3·3	3·6	3·9	4·2
6	134	162	1·5	0·9	8·9	18·0
7	166	199	5·1	4·3	3·2	6·3
8	214	251	5·5	4·1	3·9	6·1
9	141	196	4·5	4·7	3·1	4·1
10	115	225	3·2	3·0	3·6	7·5
11	247	263	4·3	4·7	5·7	5·6
12	145	193	2·7	1·9	5·4	10·2
13	207	244	4·3	4·2	4·8	5·8
14	145	145	4·2	4·2	3·5	3·5
15	104	125	4·9	5·2	2·1	2·4

Eight observations on the effect of squatting on systemic blood flow were made in squatters (Table III). In all but one, the flow increased. The mean percentage increase for the whole group was 24 and the maximum 100. The changes in the arterio-venous oxygen difference were small and inconstant in this group as in the controls (Table II), the mean change being only 0·2 ml./100 ml.

TABLE III

EFFECT OF SQUATTING ON OXYGEN CONSUMPTION, ARTERIO-VENOUS DIFFERENCE AND BLOOD FLOW. SQUATTERS

Case No.	Oxygen consumption (ml./min.)		*a*−*v* difference (ml./100 ml.)		Systemic flow (l./min.)		Effective pulmonary flow (l./min)	
	Supine	Squatting	Supine	Squatting	Supine	Squatting	Supine	Squatting
18	164	172	4·1	3·5	4·0	4·9	2·0	2·2
19	186	238	3·5	3·9	5·3	6·1	5·5	6·2
20	325	410	4·2	5·2	7·7	7·9	6·8	7·0
21	162	318	4·5	4·4	3·6	7·2	2·7	5·1
22	230	203	4·0	4·9	5·8	4·2	2·3	1·8
23	140	195	4·9	5·3	2·9	3·7	2·9	3·7
24	227	249	8·0	7·6	2·8	3·3	2·3	2·8
25	98	124	3·3	3·3	3·0	3·8	2·4	3·0
26	190	176	—	—	—	—	2·6	2·8
27	231	209	—	—	—	—	7·2	4·9

The major alterations in systemic flow were associated with oxygen consumption changes (Table III). Again, there was no relationship between the initial levels of the arterio-venous oxygen difference on the one hand, and the changes occurring with squatting on the other; nor were the changes in the one related to the changes in the other.

The changes in oxygen consumption of the squatters and the control subjects were selected for comparison, as the most data were available for this parameter, and no assumptions had to be made in its measurement. There was a mean increase of 21 per cent in the squatters and 20 per cent in the controls. The difference between these means is obviously not significant ($P>0.9$).

The effective pulmonary blood flow was increased in eight out of ten squatters (Table III). In the two control subjects with veno-arterial shunts the effective pulmonary flows increased from 2·4 to 4·0 and from 3·0 to 4·2 l./min. respectively. In the patients with no veno-arterial shunts, the effective pulmonary flow was, of course, identical with the systemic, the changes in which have already been discussed.

In the seven control subjects and the six squatters in whom there was also an arterio-venous shunt, the changes in the total pulmonary blood flow and in the arterio-venous shunt were variable and inconstant, although frequently considerable in extent. In the control subject in whom it was present at rest, the veno-arterial shunt became larger with squatting. There was an increase in the veno-arterial shunt of 1·2 l./min. in the squatter who doubled his systemic flow, a decrease of 1·1 l./min. in the patient whose systemic flow decreased, increases of less than 1·0 l./min. in two further patients, and no change in the remainder.

The effect of squatting on effective pulmonary blood flow was measured in three squatters and two control subjects who had been anæsthetized for angiocardiography. It increased in one squatter, but was reduced in all the others, the mean decrease in the five patients being 9 per cent (Table IV).

TABLE IV

EFFECT OF SQUATTING ON CARDIAC DYNAMICS. SUBJECTS INVESTIGATED WHEN ANÆSTHETIZED FOR ANGIOCARDIOGRAPHY

Case No.	Position	O_2 consumption (ml./min.)	O_2 content of R.A. blood (ml./100 ml.)	Effective pulmonary flow (l./min.)
16	Supine	171	21·1	2·2
	Squatting	207	19·1	2·1
17	Supine	88	22·8	1·6
	Squatting	108	19·8	1·4
28*	Supine	156	18·0	2·1
	Squatting	116	17·6	1·5
29*	Supine	169	24·6	4·3
	Squatting	204	24·6	6·0
30*	Supine	144	17·4	4·4
	Squatting	150	14·3	2·3

* Squatters

The pulse rate increased by a mean of 2 beats a minute in the control subjects (S.D. of change $= \pm 7$ beats/min.) and by 3 beats a minute in the squatters (S.D. of change $= \pm 4$ beats/min.). The alterations in systemic and pulmonary blood flows resulted almost entirely, therefore, from changes in stroke volume.

The effect of squatting on the oxygen saturation of blood from the upper and lower parts of the body was estimated by comparing the oxygen content of superior and inferior vena caval blood in the supine and squatting positions. The effect on inferior vena caval blood was variable, the mean change being only −0·04 ml./100 ml. In the control subjects the oxygen content of superior vena caval blood was reduced by a mean of 0·1 ml./100 ml. The changes were not consistent; there was an increase in four subjects and a decrease in four others. In contrast, increases of 0·3 to 1·8 ml./100 ml. were observed in six out of seven squatters, the superior vena caval oxygen content remaining unchanged in the one exception: these changes were highly significant (mean increase $=1.0$ ml./100 ml., $n=7$, $t=3.84$, $0.01>P>0.001$).

The effect of squatting on right atrial pressure was measured in 14 patients and the effect on pulmonary capillary venous pressure in 9. Five of these were squatters. The right atrial pressure

showed a sharp initial rise of from 2 to 8 mm. Hg with squatting, the change taking place simultaneously with raising of the legs. It was followed by a fall to 1 to 2 mm. Hg above the control level, and this slight elevation persisted as long as the squatting posture was maintained. When the legs were lowered, the right atrial pressure fell, either to the control level, or very near to it. The changes in pulmonary capillary venous pressure were similar in extent and in timing. In either case there was no obvious difference between the response of the squatters and the control subjects.

In twelve subjects, two of whom were squatters, a total of 21 recordings of the effect of squatting on arterial blood pressure were made. The changes observed are illustrated in Fig. 1. There was

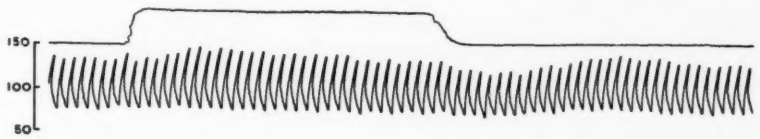

FIG. 1.—Effect of squatting on brachial artery pressure. The upward deflection of the indicator line denotes the onset of squatting: the downward deflection indicates resumption of the supine position.

an immediate increase in systolic and diastolic pressures on 18 occasions, and in pulse pressure on 17. This was followed by a gradual decline over three or four beats, phasic and pulse pressures stabilizing at about the control value or a very little above them. When the supine position was resumed, there was a further slight fall in phasic pressures, usually to below the initial levels, the pulse pressure remaining more or less unchanged. In the course of about a further ten beats the blood pressure stabilized at approximately the initial control level. These changes were slight and somewhat inconstant in the children, but greater in extent and much more constant in the three adults in the series, none of whom was a squatter, and in whom seven of the observations were made.

DISCUSSION

The patient with acyanotic congenital heart disease is able, at the cost of an increase in cardiac work, to maintain a systemic blood flow that is normal in amount and oxygen content. The patient with cyanotic congenital heart disease is at an extra disadvantage. Cardiac work is increased and, although the amount of blood reaching the tissues is normal in amount (Brotmacher and Deuchar, 1956), its oxygen content is reduced. It has been shown (Ernsting and Shephard, 1951, Holling, 1952) that, as a result of the polycythæmia, the removal of a given volume of oxygen from the blood during its passage through the capilliaries results in a relatively small drop in the percentage saturation of hæmoglobin. When the arterial oxygen content is below 80 per cent, the fall in oxygen tension between artery and vein is further minimized, owing to the form of the oxyhæmoglobin dissociation curve.

These compensatory mechanisms are only partly effective. In all but the mildest cases, despite a reduction in the arterio-venous difference, the resting percentage saturation of mixed venous as well as arterial blood is low (Holling, 1952). The capillary oxygen tension and, therefore, the tissue oxygen tension are correspondingly reduced, even at rest. It is against this background that the changes produced by squatting have to be viewed. Any benefits would, in the last resort, have to be associated with an increase in capillary oxygen tension, a decrease in cardiac work, or both.

The systemic blood flow was increased with squatting in most patients, both squatters and control subjects. The effective pulmonary blood flow and the veno-arterial shunts increased to approximately the same extent in the squatters, the arterial oxygen, which depends on the ratio of the shunt flow to the effective pulmonary flow, not being affected.

It is possible that, while the squatting position is adopted, blood is expressed from the legs, accounting for the momentary sharp rise in right atrial pressure. The increase in systemic flow may

therefore be initiated by ventricular response to greater diastolic filling. The subsequent maintenance of the increase cannot, however, be related to increases in venous return from the legs, where the blood flow is reduced as a result of the obstruction to venous return that has been shown to be associated with squatting (Brotmacher, 1957*b*). The greater systemic flow cannot be secondary to expulsion of blood from venous reservoirs in the legs, as suggested by Lurie (1953), as the obstruction to venous return produced by squatting must, if anything, be associated with pooling of blood in the legs. Reducing the venous return from the legs by squatting might be expected to have an effect comparable to that produced by inflating cuffs on the thighs, although less in extent, as the obstruction to venous return is only partial. Inflating cuffs on the thighs has been shown, as would be expected from Starling's law, to reduce cardiac output (McMichael and Sharpey-Schafer, 1944). Starling's law, however, has been found of late to be inadequate as a sole explanation of the relation of cardiac output to venous return. Stead and Warren (1947) for instance, were able to produce simultaneous increases in cardiac output and reductions in venous return. They obstructed the arterial supply to the limbs by means of tourniquets, and when these were released, the reactive hyperæmia was associated with a considerable increase in cardiac output, even when the venous return was simultaneously reduced by inflating another set of cuffs placed proximally on all limbs to a pressure of 30 mm. Hg. These observations show that factors other than the diastolic filling pressure can regulate the output of the heart.

Sarnoff and Berglund (1954) have recently modified Starling's law, introducing the concept of a " family of curves " relating ventricular stroke work to atrial pressure. They have shown in dogs that there is a close correlation between the two. When conditions are altered drastically, e.g. by administration of adrenaline, there is still a close relationship, but the curve relating the two is at a different level. The response of the heart is altered so that it may perform more work at a lower filling pressure, or less work at a higher level. Changes in atrial pressure will still, however, result in corresponding changes in stroke work.

When a patient squats, the partial obstruction to venous return from the lower half of the body tends to produce a lowering of the cardiac output. This probably accounts for the fall in systemic blood flow with squatting that was observed in two unanæsthetized patients and for the fall in effective pulmonary flow seen in four of the five patients anæsthetized for angiocardiography. The depth of anæsthesia was such that responses to external stimuli, although not abolished, were reduced considerably.

In most patients, squatters and controls alike, these tendencies are counteracted. The departure from the resting state associated with the change from the supine to the squatting position results in an increase in the cardiac output that is independent of changes in venous return. The heart, so to speak, moves to a different member of Sarnoff's family of curves. The increases in systemic flow are in this respect analogous to the increases in cardiac output in association with a reduction in venous return that were demonstrated by Stead and Warren (1947). Consequently, the higher right atrial and pulmonary capillary venous pressures observed throughout the period of squatting are probably not related causally to the increased systemic flow. They may be secondary to it or may result from changes in the pressure volume relationships of the atria.

The blood pressure changes with squatting that were observed are qualitatively similar to those described by Sharpey-Schafer (1956) in association with squatting while erect. The initial increase in systemic blood pressure with squatting is thought to be secondary to the increase in systemic blood flow. The subsequent blood pressure fall towards control levels is attributed to vaso-dilatation occurring as a baroreceptor response to the increase in pulse pressure. That this is slight and transient is immaterial. Sharpey-Schafer (1953) has shown that vaso-dilatation occurs in response to a single cough transient.

Vaso-dilatation is normally associated with increased blood flow and, in fact, a rise in forearm flow with squatting in the upright position has been demonstrated by Sharpey-Schafer (1956). It has also been found to occur when subjects squat when supine, an increase in forearm flow being observed in control subjects on ten occasions out of eleven and in squatters on nine occasions out

of eleven (Brotmacher, 1957*a*). Squatting therefore results in a redistribution of the blood flow, which is reduced in the lower part of the body and increased in the upper.

Increases in right ventricular work are proportional to increases in overall systemic blood flow. Owing to the fall in leg blood flow, the rise in blood flow in the upper half of the body with squatting must exceed the overall rise in systemic flow and be relatively greater than the rise in cardiac work. There is, therefore, a relative economy in cardiac work.

Children who are habitual squatters can adopt the position effortlessly, whereas control subjects, unaccustomed to the posture, find it somewhat uncomfortable and progressively more difficult to maintain. These differences are most obvious when patients squat while upright, but were clearly evident when observations were being made on the effect of squatting while supine. In the control subjects, the difficulty in squatting results in a general increase in muscle tone and movement. This is thought to account for an increase in oxygen requirements and a consequent absence of any consistent increase in the oxygen content of venous blood from the upper half of the body, despite the increase in systemic flow. In the squatters, on the other hand, there is little or no increase in muscle tone or activity, apart from in the legs, and, therefore, little or no rise in oxygen requirements. Consequently, in these patients, increase in blood flow in the upper part of the body with squatting is associated with a consistent increase in the oxygen content of superior vena caval blood.

The increase in blood flow to the upper half of the body with, in the squatters, a reduction in the coefficient of oxygen utilization and an increase in the oxygen content of superior vena caval blood signifies an increase in capillary oxygen tension in that part of the body. The absence of changes in arterial oxygen is relatively less important as capillary oxygen tension is related more closely to venous than to arterial oxygen tension (Barcroft, 1934).

The lessening of the anoxia in the part of the body that contains the vital centres and is the most sensitive to anoxia is accomplished with a relative economy in cardiac work. It is thought to account for the increased well-being associated with squatting, and to explain the tendency for patients with severe forms of cyanotic congenital heart disease to squat independently of exertion.

Summary

The reasons why children with severe forms of cyanotic congenital heart disease tend to squat continuously while recumbent have been investigated. Squatting results in an increase in systemic blood flow in habitual squatters and in control subjects. In patients with cyanotic congenital heart disease the rise in systemic blood flow is usually the result of an increase in both the effective pulmonary blood flow and the veno-arterial shunt. Squatting reduces the blood flow in the legs: there is a redistribution of the output of the heart as a result of which the increase in systemic flow is confined to the upper part of the body.

In habitual squatters the increased systemic flow is not associated with a corresponding rise in tissue oxygen requirements and there is consequently, in the upper part of the body, a lessening of the arterio-venous oxygen difference. The oxygen content of arterial blood remains unchanged, but that of venous blood increases and capillary and tissue oxygen tension are therefore raised. This reduction in anoxia in the part of the body that contains the vital centres and is the most sensitive to oxygen lack is thought to be the basis of the benefits obtained by patients with cyanotic congenital heart disease who squat continuously while recumbent.

I should like to thank Dr. Maurice Campbell for his advice and help in this investigation.

Appendix

The possibility that the beneficial effects of squatting are partly secondary to abdominal compression was suggested by Lurie (1953), who considered this factor important when subjects squat in the upright position. He thought that squatting results in compression of reservoirs of blood in the abdomen as well as the legs; it thus counters the effects of gravity, which causes a fall in cardiac output in the erect position, owing to pooling of blood in the lower half of the body.

The effect of squatting in the supine position on intra-abdominal pressure was investigated in five patients with pulmonary tuberculosis in whom this pressure was measured before pneumoperitoneum refills. Squatting resulted in pressure increases of 4 to 8 mm. Hg. It was found that increases of this order could be produced by inflating a cuff applied to the abdomen to a pressure of 50 mm. Hg. This method was then used to study the effects of abdominal compression on blood flow in the arms and legs and on the overall systemic flow. These were measured by venous occlusion plethysmography and at cardiac catheterization respectively.

None of the effects of squatting could be reproduced by abdominal compression. In four squatters and six control subjects the mean blood flow in the legs was *increased* by 0·2 and 0·1 ml./100 ml. respectively. Forearm flow was increased in a group of eight control subjects, but the mean change was very small and not significant (mean increase=0·2 ml./100 ml., $t=1·0$, $0·4>P>0·3$). In six control subjects, the overall systemic blood flow was *reduced* significantly by abdominal compression (mean reduction=16%, $t=3·61$, $0·02>P>0·01$), which probably has an effect on the venous return similar to that of cuffs on the thighs.

It is concluded that the beneficial effects of lying continuously in a squatting position are not related to the small increase in intra-abdominal pressure that is produced.

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HÆMODYNAMIC EFFECTS OF SQUATTING DURING RECOVERY FROM EXERTION*

BY

LEON BROTMACHER

From the Cardiac Department, Guy's Hospital

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The hæmodynamic changes that are thought to account for the continuous adoption of a squatting position by patients with cyanotic congenital heart disease have been discussed (Brotmacher, 1957*b*). The present study is concerned with the effects of squatting during recovery from exertion, and was undertaken in an attempt to explain the tendency of these subjects to squat for periods of two to ten minutes when they have become tired and breathless as a result of effort. The effects of squatting on the circulation in the legs and on the anoxia of cyanotic congenital heart disease have been investigated, and the relationship between the two is discussed.

Effect of Squatting on the Circulation in the Legs

The effect of squatting on the venous pressure in the legs was measured in four medical students. A 21-gauge needle was inserted into a vein on the dorsum of the foot and connected to a Southern Instruments Minirack capacitance electromanometer by plastic tubing of 2 mm. internal bore. Another length of plastic tubing, filled with saline, was connected at one end to the manometer and strapped to the ankle at the other, which was open to the atmosphere. It was thus possible to register alterations in the height of the foot relative to the manometer and to apply the appropriate corrections. After control observations had been made with the patient supine, the venous pressure in the leg was measured with the subject in the squatting position. The thighs were passively flexed, slightly abducted and laterally rotated at the hips, and flexed at the knees, the thighs being brought as near as possible to the flanks. Squatting raised the venous pressure on all four occasions, the increases ranging from 10 to 28 mm. and averaging 20 mm. Hg. With resumption of the supine position the pressure fell to about the initial control levels. While in the supine position, one subject was able to raise the venous pressure in his foot by about 16 mm. Hg on three occasions by tensing his leg muscles to the greatest extent possible.

The changes in arterial blood pressure in the legs with squatting were measured by palpation, using the posterior tibial pulse, and by the flush method (Reinhold and Pym, 1955). In order to eliminate the possibility of any underlying general change, control measurements with the legs extended were made both before and after squatting. These measurements were averaged when calculating the pressure changes produced by squatting. Nine squatters and ten control subjects were studied. In both groups the systolic pressure fell by comparable amounts, the decrease ranging from 3 to 58 and averaging 18 mm. Hg. Good agreement between the two methods employed was obtained, the pressures as measured by the flush technique being slightly lower than those measured by palpation.

Blood flow through the leg was measured by venous occlusion plethysmography, the method being essentially that of Grant (1937–8). The subjects rested on the couch for at least half an hour before the first observations were made, the head and shoulders being supported on pillows

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and the legs extended. No attempt was made to regulate the room temperature; in practice it was always between 20° and 24° C.

The squatters were all patients with Fallot's tetralogy, their ages ranging from six to fifteen years. The controls on whom the effects of squatting were measured were children of from five to twelve years of age with acyanotic congenital heart disease or with non-cardiac conditions.

The squatting position was adopted as already described except that full flexion of the knee was not possible when the plethysmograph was on the leg. When the effects of varying degrees of venous occlusion on leg blood flow were being studied, a 12×40 cm. thigh cuff was placed on the upper part of the thigh. Repeat control observations were always made after measuring the effect of any particular manœuvre on blood flow, and the results were only considered acceptable if an increase in blood flow with the manœuvre was followed by a decrease when the final control observations were made, or vice versa. However, an exception was made when the changes with squatting were very small and the two control observations did not differ by more than 1·0 ml./100 ml./min. The mean of the two control observations was used in calculating changes.

Six observations of the effect of squatting on blood flow in the legs were made in squatters. It was reduced on every occasion (Table I), the change varying from 15 to 55 per cent with a mean of

TABLE I

EFFECT OF SQUATTING ON BLOOD FLOW IN LEGS

Case No.	Leg blood flow (ml./100 ml./min.)			Percentage change	Case No.	Leg blood flow (ml./100 ml./min.)			Percentage change
	Supine	Squatting	Supine			Supine	Squatting	Supine	
	1. *Squatters*					2. *Controls*			
22	4·3	3·2	5·0	−32	43	3·0	2·0	4·1	−44
23	9·1	7·4	7·9	−13	44	2·8	1·7	2·9	−41
33	2·7	1·4	3·5	−55	45	6·3	5·2	5·5	−12
40	3·7	3·2	4·1	−18	46	4·3	3·6	5·0	−23
41	3·9	3·1	3·3	−15	47	1·9	1·3	1·3	−19
42	4·0	3·0	4·1	−27	48	2·7	2·0	2·5	−23
					49	3·0	2·4	2·5	−14
					50	4·7	4·5	6·5	−20
					51	3·6	3·1	3·6	−14
					52	6·8	5·7	6·9	−18
Mean change			−1·1	−27	Mean change			−0·9	−23

$t=5·90$; $n=6$; $0·01>P>0·001$. $t=6·45$; $n=10$; $P<0·001$.

27 per cent. Ten observations were made in control subjects, in all of whom there was a reduction in blood flow, varying from 12 to 44 per cent, the mean reduction in this group being 23 per cent (Table I). In both groups, the difference between the squatting and the supine levels is highly significant. The difference between the effects of squatting on the leg blood flow observed in the squatters and the control group is very small and not significant (difference between mean changes =0·2 ml./100 ml./min., $t=0·87$, $n=16$, $0·4>P>0·3$), or in their variability (variance ratio (F)= 1·02, 10% level of $F=2·9$).

In order to determine whether the reductions in leg blood flow with squatting were the result of general or local changes, the effect of putting the left leg into the squatting position on the blood flow in the right one was measured. Five observations were made in squatters and five in control subjects. The changes were inconstant: the blood flow increased on three occasions in the squatting group and decreased twice. There were increases in two control subjects and decreases in three. The mean blood flow *increased* slightly with one leg in the squatting position.

The effect of varying degrees of obstruction to the venous return from a limb was next measured, a cuff proximal to the venous occlusion cuff being inflated to a pressure of 25 mm. Hg, corresponding approximately to the increase in venous pressure in the legs associated with squatting. Four observations were made in control subjects. Inflating the cuff produced falls in blood flow of 31, 33, 45, and 59 per cent. The mean fall was 39 per cent, which is over 15 per cent more than the mean fall in leg blood flow produced by squatting in the control subjects and the squatters

when considered jointly (Table I). Although the group studied was very small, the reduction in blood flow produced by the cuff inflated to 25 mm. Hg is significant($t=4{\cdot}3$, $0{\cdot}05>P>0{\cdot}02$).

Effects of Squatting on Arterial Oxygen Saturation

By means of ear oximetry it is possible to measure the percentage oxygen saturation of arterial blood continuously without subjecting the patient to the discomfort of arterial puncture. The instrument employed in the present investigation was the Stanco oximeter, based on the design of Stott (1953).

Observations were made on nine squatters aged five to twenty and on three patients aged five to nine who had cyanotic heart disease but did not squat. Control observations were made with the patients standing until conditions were stable. The effects of squatting or exercising were then observed. The patients exercised by climbing on and off a step six inches high.

The patients were exercised until their arterial oxygen saturations had fallen by ten per cent, or until they felt that they could not continue without discomfort. They then stood still and the arterial oxygen saturation was noted every quarter of a minute during recovery. After an adequate rest the exercise was repeated, and the arterial saturation during recovery was observed with the patient in a squatting position. No attempt was made to standardize quantitatively the amount of work done, but to ensure that the two tests were comparable, the exercise on the second occasion was continued until the arterial oxygen had fallen to the level reached at the end of the first period of exercise.

The arterial oxygen saturation was little changed in nine squatters when standing and when squatting, ten observations being made in all; no differences of more than two per cent were seen, and in five subjects there were no differences at all (Table II). In contrast, the effect of squatting

TABLE II

Effect of Squatting on Percentage Oxygen Saturation of Arterial Blood

Oximetric observations on squatting

Case No.	Percentage saturation of arterial blood		
	Standing	Squatting	Standing
22	61	61	62
23	94	93	95
27	86	86	86
34	95	95	95
35 {	92–93	90–91	92–93
	92–93	90–91	92–93
36	74	75	75
37	90	90	90
38	74	74	74
39	87	85	87

on the saturation during recovery from exercise was quite dramatic in the patients who were habitual squatters (Fig. 1). When they stood at the conclusion of the exercise, the arterial oxygen saturation continued to fall, reaching its nadir about half a minute afterwards. Only then did it start to rise, reaching the level observed at the moment of conclusion of the exercise after the expiry of about a further half minute; it was, therefore, a minute after the exercise before it began to rise above the level at the end of exercise. When the patient squatted at the end of the exercise, the rate of recovery of the arterial oxygen saturation was no greater than when standing; but it no longer fell after the exercise ended and started to rise from the moment when it ended. The arterial oxygen saturation reached at any point in time with the patient squatting was reached only about a minute to a minute and a half later when standing during recovery. Between a quarter of a minute and two minutes after ending the exercise, the saturation with the patient squatting was anything up to

twelve per cent higher than while standing. Ten observations were made and the differences were apparent in all but one.

Irrespective of whether the patient stood or squatted during recovery, the rate of increase in arterial oxygen saturation lessened as the resting level was approached, but the percentage was occasionally slightly greater after recovery than it had been before starting the exercise (Fig. 1).

The continued decline in the arterial oxygen saturation when the patient stood at the end of the exercise—a feature that has often been demonstrated by Campbell in such patients—and the relative

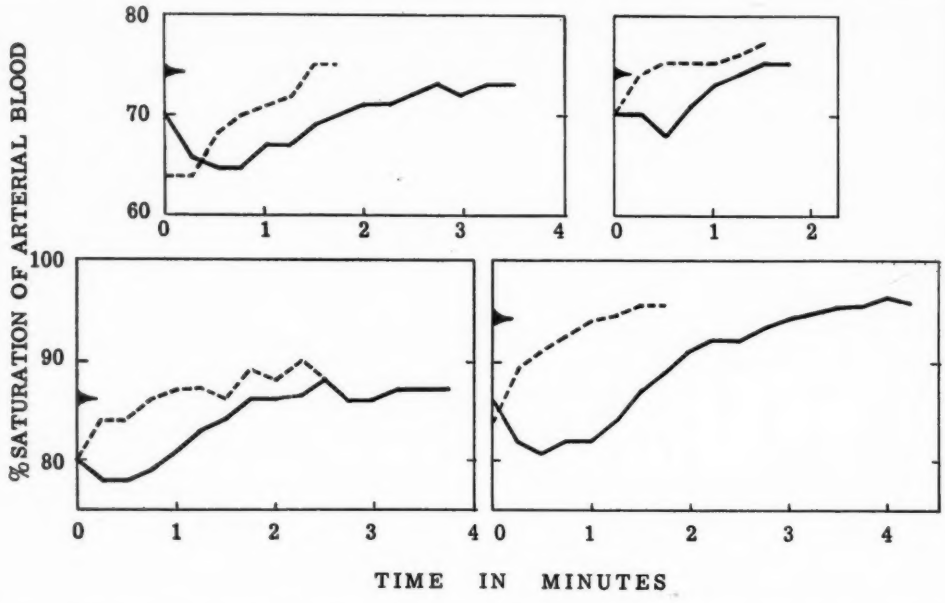

FIG. 1.—Effect of squatting on arterial oxygen saturation in four patients during recovery from leg exercise. Oximetric observations on squatters.

The continuous lines indicate the changes with standing. The interrupted lines indicate the changes with squatting and show an immediate rise and a quicker return to normal.

The arrow heads on the ordinates indicate the initial resting levels.

increase in saturation associated with squatting could often be detected clinically. The patients themselves, when questioned, admitted to greater discomfort when standing than when squatting.

The effects of standing and squatting during recovery from exercise were compared in three non-squatters with cyanotic congenital heart disease. The differences that have been described in the case of the squatters were not observed (Fig. 2a). Irrespective of whether the patients stood or squatted after exercising, the arterial oxygen saturation continued to fall during the first half minute or so of the rest period, and did not rise to the level that was present at the end of the exercise until after about another half minute. Squatting did not appear to have any effect on the arterial oxygen saturation during any part of the recovery period.

In two squatters in whom arterial oxygen desaturation was produced by vigorous upward and downward movement of the arms, the rate of recovery from the moment of ending the exercise was not affected appreciably by squatting (Fig. 2b). Additional observations could not be made, as the remaining subjects were unable to continue the exercise owing to muscular fatigue, even though their arterial oxygen saturations had not fallen appreciably.

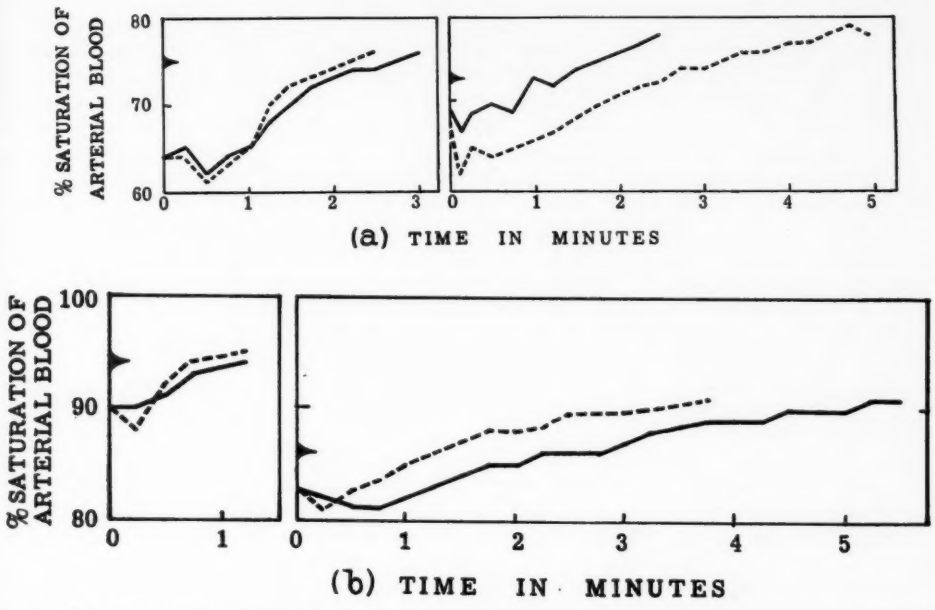

FIG. 2.—Effect of squatting on arterial oxygen saturation. Oximetric observations during recovery from exercise.
(a) Two control subjects with cyanotic congenital heart disease. Leg exercise.
(b) Two squatters. Arm exercise with patients standing.

The continuous lines indicate the control observations. The interrupted line indicates the changes with squatting and fail to show the improvement that was seen in Fig. 1.

The arrow heads on the ordinates indicate the initial resting levels.

DISCUSSION

When a patient squats, the femoral arteries and the femoral veins become angulated acutely in the groins, where they pass between the inelastic inguinal ligaments and the superior pubic rami. The popliteal arteries and veins are similarly angulated in the popliteal fossæ. The muscles of the legs are in tonic contraction and there is some increase in the tone of the muscles of the anterior abdominal wall, against which the thighs are pressed. The slight fall in arterial pressure in the legs observed in the present investigation is thought to be secondary to such kinking of the main arteries of the legs in the groins and behind the knees. The rise in venous pressure could be due to venous kinking in the groins and popliteal fossæ, or to pressure on the veins by muscles in tonic contraction. Kinking of the veins is probably the more important, as voluntary tonic muscle contraction produces rises in venous pressure comparable with those associated with squatting only when the leg muscles are tensed to the greatest possible extent.

The reduction in the blood flow in the legs with squatting is an expected consequence of the reduction in the arterial and the increase in the venous pressures. Obstructing the venous return from a limb by inflating a cuff to 25 mm., which is about the average increase in venous pressure observed with squatting, produced falls in limb blood flow comparable to those produced by squatting. This indicates that the increase in venous pressure with squatting can, by itself, bring about the reduction in leg blood flow. Once a local cause for the change in leg blood flow with squatting is accepted, the absence of any difference between the changes observed in the squatters and in the control subjects becomes quite understandable. As far as the anatomy of the great

vessels in the legs is concerned, patients with cyanotic congenital heart disease do not differ from others.

At rest there is no special difference between the oxygen content of blood from the legs and that from the rest of the body. On five occasions samples obtained from the bifurcation of the inferior vena cava or from a common iliac vein showed a percentage oxygen saturation of from 64 to 85 per cent. Reduction in the extent of its contribution to the mixed venous blood is unlikely, therefore, to affect the oxygen saturation of the latter appreciably. On the other hand, with exercise, the oxygen saturation of iliac vein blood falls precipitously: on four occasions it was found to be between 31 and 51 per cent after only 20 movements of foot pedals against a spring resistance. In patients with a veno-arterial shunt, mixed venous blood with correspondingly low oxygen content passes directly into the arterial stream: Davison *et al.* (1953) have shown that this accounts in very large measure for the fall in arterial oxygen saturation with exercise.

The continued fall after exercise when patients with cyanotic heart disease remain standing is probably due in large measure to the oxygen requirements of the leg muscles remaining high even after contraction has ceased. This is frequently the case when the energy requirements have been met in some measure anærobically during the period of contraction. A small part of the continued fall may also be accounted for by the time taken for blood leaving the muscles at the moment the exercise ends to reach the arteries.

McNeill (1956) has shown that, after exercise, vaso-dilatation of muscle arterioles persists after the excess oxygen requirements have been met, the oxygen content of venous blood from the muscles rising towards arterial levels. This may well account for the arterial oxygen saturation of some of the patients in the present investigation rising to above the initial resting levels at the end of the recovery period.

The present investigation has shown that squatting produces obstruction to the venous return from the legs. It therefore reduces the amount of desaturated femoral vein blood reaching the heart and so minimizes the tendency of the oxygen saturation of mixed venous blood to fall with exercise. This is reflected in the higher arterial oxygen saturation that has been observed, both in the present and in previous investigations (Callebaut *et al.*, 1949; Lurie, 1952, 1953), when habitual squatters squat instead of standing during recovery from exercise. The findings of Dexter (1951) and of Lurie (1953) that elastic bandages applied to the legs can obviate the need to squat can be similarly explained on the basis of obstruction to venous return. The effects of abdominal compression by means of binders, which has also been found to obviate the need to squat (Lurie, 1953) can be explained in the same way. The effect of abdominal compression on cardiac output suggests that it impedes venous return (Brotmacher, 1957*a*). A degree of obstruction to venous return too slight to produce measurable reduction in leg blood flow may well have a measurable effect on arterial oxygen saturation, when femoral venous blood is very desaturated. Callebaut *et al.* (1949) attributed the changes in arterial oxygen saturation that they observed with squatting to diminution in the veno-arterial shunt. This was not measured by them, and recent findings indicate that this shunt is not, in fact, lessened (Brotmacher, 1957*b*).

During recovery from arm exercise, the rate at which the arterial oxygen saturation returns to the resting level is not affected by squatting. This is an expected finding, as squatting cannot have any effect on the venous return from the arms.

In patients with cyanotic congenital heart disease who do not squat, the obstruction to the venous return from the legs tends to raise the arterial oxygen saturation, and the effort required to maintain an unaccustomed position tends to lower it. As a result of the interplay of these opposing factors, the arterial oxygen saturations when standing and when squatting after exercise are not appreciably different in this group.

The changes with squatting after exertion that have been described result in the capillary oxygen tension being raised in the upper part of the body, at the cost of lowering the blood supply to the legs. This is not serious, as muscles that are not actively contracting can tolerate ischæmia well. In fact, partial exclusion of the legs from the circulation is beneficial, as it reduces the amount of

work that the heart has to perform at a time when the demands upon it are maximal. The magnitude of the changes that have been observed suggest that the increases in capillary oxygen tension that result from squatting after exertion are much greater than those produced by squatting at other times.

These increases occur in the parts of the body that contain the vital centres and are the most sensitive to anoxia. They are brought about with a relative economy in cardiac work and are thought to be the basis of the subjective improvement with squatting, and to account for the habitual adoption of this position after exertion by patients with cyanotic congenital heart disease.

Summary and Conclusions

Squatting causes kinking of the femoral arteries and veins in the groins and of the popliteal arteries and veins in the popliteal fossæ. Blood flow in the legs is reduced, mainly as a result of obstruction to the venous return.

When patients with cyanotic congenital heart disease exercise, the oxygen content of femoral venous blood falls precipitously. This desaturated blood reaches the right side of the heart and is shunted into the systemic arteries. The oxygen saturation of arterial blood falls in consequence Squatting impedes the venous return from the legs and therefore minimizes the tendency of the arterial oxygen saturation to fall with exercise.

I should like to thank Dr. Maurice Campbell for his advice and help in this investigation.

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CASE REPORTS

LONGEVITY IN PATENT DUCTUS ARTERIOSUS

BY

C. W. CURTIS BAIN

From the General Hospital, Harrogate

Persistence of the ductus arteriosus is not usually associated with a normal life expectancy. All but three of 62 patients were under 40 when they died (Shapiro, 1944). Three patients, all women, have lived to over 70 years. One who died at 79 is mentioned briefly as having a small opening and great dilatation of the pulmonary arteries with general cardiac hypertrophy (Holman *et al.*, 1953). Another who lived to 75 had auricular fibrillation and congestive failure: the ductus measured 3 mm. across (Fishman and Silverthorne, 1951). Cardiac catheterization established the diagnosis in a woman aged 72 years with auricular fibrillation and congestive failure (Storstein *et al.*, 1952). Two cases are now reported, one of whom died at 85 years, and never suffered from congestive failure, while the other is living at 63.

Case 1. This patient was born in 1870 and spent her active life as a school-mistress. She was seen first in 1944, when she was 74, suffering from short paroxysms of tachycardia. The blood pressure was 180/80. The apex impulse was heaving and outside the nipple line. A continuous murmur with systolic accentuation was present in the pulmonary area, but there was no thrill. The pulmonary second sound was loud and clear. The electrocardiogram showed left ventricular hypertrophy. Screen examination showed some enlargement of the heart to the left, and the aorta was much unfolded with calcification in the aortic knob.

Later that year she was seen by Dr. James Brown who agreed with the diagnosis of a patent ductus. In 1949 she was shown to Sir John Parkinson who pointed out the calcified ductus in the left oblique view (Fig. 1). Subsequently the paroxysms of tachycardia became more frequent and lasted longer. The ductus murmur became less obvious and in 1955 only the systolic component was present. Finally in 1956, she became anæmic from gastro-intestinal bleeding and died, aged 85. She never had cardiac failure.

Necropsy (Dr. J. V. Wilson). The body was of normal development and nutrition. The heart weighed 270 g. The walls of the ventricles were of normal thickness and there was neither hypertrophy nor dilatation of any chamber. The heart valves were normal. The aorta showed extensive areas of degeneration and calcification and the ascending aorta and the arch were slightly dilated due to this degeneration. The coronary arteries were thickened and sclerosed but were nowhere occluded. The myocardium was healthy apart from some fibrosis.

The ductus arteriosus was patent. The aortic opening (Fig. 3) was funnel-shaped due to extensive calcification of the wall of the aorta. This calcification extended for a radius of about 1 cm. around the opening so that the wall of the opening itself was firm and largely calcified: it was 4 mm. in diameter. The total length of the ductus was 6·5 mm. and it was calcified for about 3·5 mm. distal to the aortic opening forming a rigid channel. The pulmonary opening (Fig. 4) was surrounded by a thin fringe of endothelium and was freely mobile on its attachment to the pulmonary artery. The main pulmonary artery showed no evidence of calcification and the pulmonary branches were not thickened.

The kidneys were contracted and granular. The bowel mucosa showed considerable congestion and the contents of the lumen were extensively blood-stained, especially in the upper part of the small intestine. There was no visible intestinal ulceration and the blood appeared to be oozing from the congested mucous membrane. Death was due to uræmia. A remarkable feature of the necropsy was the absence of evidence or circulatory embarrassment from the ductus arteriosus.

FIG. 1.—Left oblique film, showing calcified ductus. Case 1.

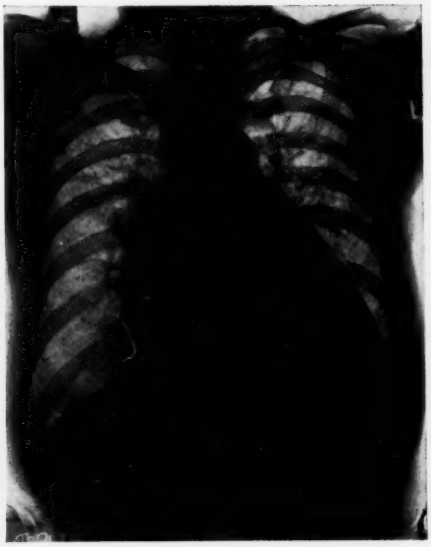

FIG. 2.—Generalized cardiac enlargement with prominence of pulmonary arc. Case 2.

FIG. 3.—Aortic opening, showing the areas of calcification and the funnel-shaped opening. Case 1.

Case 2 was born in 1892. At the age of 16 while staying with relatives in Colne she developed appendicitis and was attended by Dr. James Mackenzie who did not advise an operation on account of her heart. When seen in 1952 the pulse was collapsing and the blood pressure was 180/70. The apex impulse was heaving and 13·5 cm. to the left of mid-sternum. A continuous Gibson murmur with systolic accentuation was audible in the pulmonary area. There was no thrill. The pulmonary second sound was not audible.

FIG. 4.—Pulmonary opening with surrounding membranous fringe. Case 1.

By 1956 auricular fibrillation had supervened, but the murmur was unchanged. She was dyspnœic on exertion but was complaining chiefly of pain down her legs due to a prolapsed disc. The electrocardiogram showed auricular fibrillation and left ventricular hypertrophy. Chest films showed considerable enlargement of the heart to the left, and some prominence of the pulmonary arc (Fig. 2). The lung roots were large and some pulsation could be seen on screening.

Cardiac catheterization (Dr. E. J. L. Pearce) disclosed a moderate rise of pulmonary arterial pressure, this being 50/15 in the right pulmonary artery and 50/0 mm. in the right ventricle: the left branch of the pulmonary artery could not be entered. There was also evidence of a left-to-right shunt into the pulmonary artery, probably with some regurgitation into the right ventricle. The oxygen saturation was 89 per cent in the pulmonary artery sample, 72 per cent in the high and 56 per cent in the low right ventricular sample, and 51 per cent in the right atrial sample. In view of the absence of the pulmonary second sound it seems likely that this increased oxygenation of the right ventricle was due to pulmonary incompetence. The systemic flow was calculated as 3·4 litres a minute and the pulmonary flow (20·9 litres) and shunt were very large but difficult to assess accurately as the high saturation of the pulmonary artery suggested this had been sampled near the ductus before there was much mixing.

Summary

Two cases of patent ductus arteriosus are described. One survived to the age of 85 years and never suffered from cardiac embarrassment. The other, with some rise of pulmonary arterial pressure and incompetence, is still active at 63 years.

I am indebted to Dr. J. V. Wilson for the autopsy report and for the photograph of the ductus.

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THE WENCKEBACH PHENOMENON ASSOCIATED WITH SIALORRHŒA

BY

E. CHESLER AND L. SCHAMROTH

From the Baragwanath Hospital, Johannesburg

The Wenckebach phenomenon (1899) is a not uncommon form of partial A-V block and is usually associated with organic heart disease. Variations of this pattern have been described but are rare. We report here another variant of the Wenckebach phenomenon in a patient who complained only of sialorrhœa and showed no evidence of organic heart disease.

Case Report

A 23-year-old African male labourer stated that for the previous two years he had been troubled by periods of excessive salivation. These periods varied from a few days to several weeks with symptom-free intervals of similar duration. This excessive salivation necessitated the frequent use of a handkerchief, and on awakening, his pillow was often wet. There were no other symptoms. He had never experienced any syncopal attacks, nor was he prone to palpitations. He had no exertional dyspnœa and was able to complete a day of strenuous manual labour without discomfort. There was no history of rheumatic fever and he had not been taking drugs.

Physical examination showed a well nourished man. His blood pressure was 120/75 mm. Hg. Apart from occasional dropped beats detected at the pulse and on cardiac auscultation, there were no other abnormalities.

Full blood count and sedimentation rate were normal. C-reactive protein was absent.

Oral glucose tolerance curve showed a tendency to rebound hypoglycæmia: Fasting specimen—67 mg. per 100 ml. Post ingestion specimens: ½, 1, 1½, 2, 3, 3½, 4, 5, 5½, and 6 hours were, 126, 160, 127, 105, 65, 43, 50, 73, 75, and 77 mg. per 100 ml.

Teleradiogram and fluoroscopy revealed a normal heart shadow and normal lung fields.

Electrocardiograms showed the varying type of Wenckebach phenomenon (see Fig. 1, 2, and 3).

Complete relief of the sialorrhœa was afforded by the oral administration of tincture of belladonna, 10 minims thrice daily.

Discussion

In the classical Wenckebach type of A-V block the P–R interval shortens considerably after a beat is dropped and then lengthens progressively from cycle to cycle until conduction fails once again. A "reverse" Wenckebach phenomenon is described by Berman (1955). This consists basically of a 2:1 A-V block associated with decreasing P–R intervals and ending in an occasional 1:1 conducted beat with a prolonged P–R interval: examples occurred as transient events in five patients, four of whom had posterior myocardial infarction and the other rheumatic carditis with aortic insufficiency. Furthermore, this arrhythmia was associated with a bad prognosis in the cases described. Another modification, reported by Scherf and Schott (1939) and Mack *et al.* (1947), was made up of a basic 1:1 conduction with diminishing P–R intervals ending in a non-conducted beat. Solinas and Sardo (1952) described fluctuations in the length of the P–R intervals which increase and decrease without dropped beats. Pallini *et al.* (1951) recorded a case in which the orderly progression of the Wenckebach pattern was interrupted by a short P–R interval followed by a broad QRS complex of the Wolff-Parkinson-White type. In a case described by Simonson and Berman (1951), paroxysmal auricular tachycardia and partial A-V block were associated with diminishing P–R intervals. Segers (1951) recognized a 2:1 A-V block in which the P–R intervals of the conducted beats varied from 0·14 to 0·21 sec.

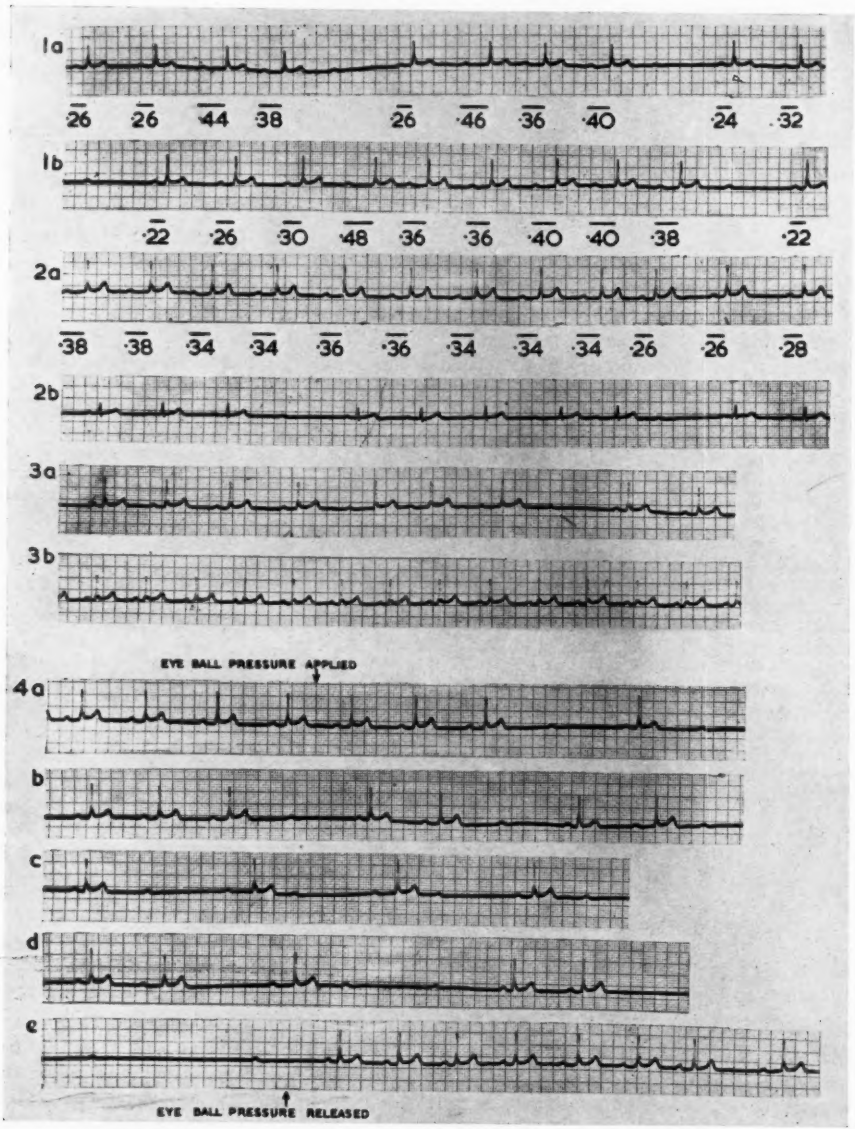

FIG. 1a: 7/3/56.—Standard lead II, showing the varying Wenckebach phenomenon, namely, varying P–R intervals with irregularly dropped beats (measured P–R intervals indicated).

FIG. 1b: 10/7/56.—Standard lead II, showing the varying Wenckebach phenomenon (measured P–R interval indicated).

FIG. 2a: 20/7/56.—Standard lead II: basic rhythm, showing minor variations in the P–R intervals without dropped beats as described by Solinas and Sardo. The normal sinus P waves are constant in shape and size (measured P–R intervals indicated).

FIG. 2b: 20/7/56.—Lead AVF: The varying Wenckebach phenomenon induced by the intramuscular injection of 0·5 mg. prostigmine. This change occurred from the basic rhythm as shown in Fig. 2a.

FIG. 3a: 21/7/56.—Standard lead II, showing the varying Wenckebach phenomenon induced by carotid sinus pressure.

Mobitz (1924, 1928) defined the Wenckebach phenomenon as Type I A-V block. His Type II A-V block, now known as the Mobitz block, consisted of irregularly dropped beats without previous lengthening of the P–R interval.

The electrocardiogram of the case presented here shows some of the features of the classical Wenckebach phenomenon in that from an initially shorter P–R interval, progressive lengthening occurs (Fig. 1a, 1b, 2b, and 3a). However, this progressive lengthening is not maintained, as P–R intervals of shorter duration are interspersed. These variations in the P–R intervals do not conform to any particular pattern and do not follow any logarithmic sequence. The dropped beat does not necessarily follow the cycle with the longest P–R interval. The P–R interval following the dropped beat is, however, always the shortest. This pattern was observed during episodes of sialorrhœa (Fig. 1a and 1b) and could be provoked by parasympathetico-mimetic measures such as eyeball pressure, carotid sinus pressure (Fig. 3a) and the injection of prostigmine (Fig. 2b). The dropped beats were easily abolished by the intravenous injection of atropine gr. 1/100 (Fig. 3b) although slight variations in the P–R intervals were still evident. This increase and decrease in the P–R intervals without dropped beats (as described by Solinas and Sardo) and with normal sinus P waves of constant size and shape, was present as a basic abnormality (Fig. 2a). It was only with further increase in vagal tone occurring spontaneously during periods of sialorrhœa or as a result of the use of parasympathetico-mimetic measures that dropped beats reappeared. The effect of vagal stimulation is further demonstrated by the occurrence of S–A block, ventricular standstill, the classical Wenckebach phenomenon, and the "reverse" Wenckebach phenomenon with these measures (Fig. 4). Marked respiratory sinus arrhythmia was also observed.

The oral glucose tolerance curve showed a strong tendency towards rebound hypoglycæmia three and a half hours after the ingestion of 50 g. glucose. This is due to an excess of postprandial insulin secretion from the action of a hypersensitive vagus as occurs in the vagotonic subject (Conn and Seltzer, 1955). The sialorrhœa is further evidence of this excessive vagal activity.

Partial heart block with dropped beats is almost invariably associated with organic disease. It is especially seen with digitalis intoxication, rheumatic and diphtheritic myocarditis, and coronary artery disease. An acute infection such as tonsillitis often precipitates it (Campbell, 1943). It has been produced experimentally by vagal stimulation (Mines, 1914; Lewis, 1925; Rothberger, 1931), and by parasympathetico-mimetic drugs (Starr, 1936; Dercherd and Ruskin, 1946). It may occur at low auricular rates under the influence of digitalis therapy, or at higher auricular rates as with paroxysmal auricular tachycardia.

A consideration of all the features of our case suggests that variations in vagal tone may well be the common factor affecting both excitability and conductivity, thus playing an important if not the dominant role in the mechanism of partial A-V block. This case illustrates the fact that gross cardiac arrhythmias are not characteristic of any specific clinical or pathological condition and may occur in the absence of organic heart disease. Furthermore, their presence does not invariably connote an adverse prognosis.

Summary

An unusual form of the Wenckebach type of partial A-V block is described.

Other rare varieties of partial A-V block were noted in the electrocardiograms of this patient.

These disorders of cardiac rhythm occurred in a man who showed evidence of excessive vagal activity but no signs of organic disease.

Legend to FIG. 3 continued.

FIG. 3b: 21/7/56.—Standard lead II: effect after the intravenous injection of 1/100 gr. of atropine sulphate, showing change to basic rhythm from the varying Wenckebach phenomenon as shown in Fig. 3a.

FIG. 4a to e: (continuous strip), 22/7/56.—Standard lead II: effect of eyeball pressure, showing the classical Wenckebach phenomenon (the last four complexes in Fig. 4b), an arrhythmia approximating to the Mobitz Type II block (the first three complexes in Fig. 4b), the "reverse" Wenckebach phenomenon as described by Berman (1955) (the last three complexes in Fig. 4c continued to the first two complexes in Fig. 4d), S-A block and also ventricular standstill (Fig. 4d and 4e).

We wish to thank the Superintendent of Baragwanath Hospital for permission to publish this case. We acknowledge with thanks the helpful discussions with Dr. M. B. Schwartz and Dr. B. A. Bradlow. We are indebted to the Baragwanath Branch of the South African Institute for Medical Research for the laboratory investigations and to Mr. C. Shevitz of the University of the Witwatersrand, Department of Medicine for the photographic reproductions.

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PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY

Annual General Meeting

The Thirty-sixth Annual General Meeting of the British Cardiac Society was held at Adam House, Edinburgh, on Thursday, May 16, 1957. The Chairman, Rae Gilchrist, took the Chair at 9 a.m.; 134 members and 4 visitors were present.

Private Business

1. The minutes of the last Annual General Meeting, having been published in the Journal (**18**, 565, 1956), were taken as read and confirmed.
2. The Balance Sheet for 1956–57 was presented, having been audited and found correct by Baker and Crozier. The credit balance on April 18, 1957, was £605 19*s*. 6*d*. In addition the Society held £800 2½% Savings Bonds 1964/67.
3. Bruce Maclean was elected an *Extra-Ordinary Member* of the Society.
4. Dr. Mannheimer and Dr. Werkö of Stockholm were elected as *Corresponding Members* of the Society.
5. The following Associate Members were elected as *Ordinary Members*.

W. D. Brinton	R. Mulcahy
W. E. Clarke	M. F. Oliver
Sheila Howarth	A. Schott
R. F. Jarrett	P. Stock

6. The following *Associate Members* were re-elected for a further period of three years.

R. M. Fulton	T. D. V. Lawrie
C. B. Henderson	A. W. W. B. Woods

7. The following new *Associate Members* were elected and introduced to the President and Chairman:

   J. R. Belcher (London) (Surgical Member)
   G. de J. Lee (Oxford)
   C. S. McKendrick (Liverpool)
   J. Mackinnon (Manchester)
   B. B. Milstein (London) (Surgical Member)
   G. B. Shaw (Glasgow)

8. Samuel Oram and E. J. Wayne were elected *Members of the Council* in place of Crozier and Hayward (term of office expired).
9. It was agreed that Rule 23 of the Society should be altered to read:
   "The subscription shall be fixed by the Council and shall become payable on the first day of June," the remainder of the rule remaining as at present.
   It was also agreed that Rule 11 should be altered to read as follows:
   "Associate Members shall be elected for three years. Generally after this time and at the latest after six years they will not be re-elected unless they are qualified to become Ordinary Members, which will depend on their holding a position as a consultant devoted mainly to cardiology and/or their published work. They will be expected to resign if they cease to be qualified as Associate Members. They shall take part in the scientific business and may attend, but not take part in, the private business of the Society."
10. The Chairman made the following announcements. There will be an Autumn Meeting of the Society on Friday, November 29, in the Barnes Hall of the Royal Society of Medicine, London. The Annual General Meeting in 1958 will take place in Leeds and will be a two-day meeting, on Thursday and Friday, April 17 and 18, under the Chairmanship of Towers. Lastly the Third World Congress of Cardiology will take place in Brussels from September 14 to 21 under the Chairmanship of Professor Rijlant.

Symposium on Coronary Artery Disease

Some Current Views on the Ætiology of Coronary Artery Disease

By M. F. Oliver and G. S. Boyd (*introduced*), Edinburgh

Coronary disease was registered as the cause of 20 per cent of all deaths in Great Britain in 1955, and analyses of mortality rates indicated that deaths certified as angina or coronary thrombosis increased seventyfold between 1920 and 1955. A similar trend was seen from analyses of morbidity rates in the Edinburgh Royal Infirmary over the last 20 years. This increase in the incidence of the clinical manifestations of coronary disease is undoubtedly partly due to improved diagnosis in an ageing population and to changing fashions in death certification, but it is believed that much of the increase is real.

It has been customary to believe that the prevalence of the clinical manifestations of coronary disease is determined by the degree of coronary atheroma and that there is a simple and direct relationship between the clinical features and the severity of the pathological lesions. This may be an oversimplification, since analysis of the London Hospital autopsy records has indicated that the incidence of advanced coronary atheroma had not increased during the first half of this century. Moreover, the striking male predominance in the incidence of clinical coronary disease does not apply to coronary atheroma. Furthermore, actual coronary atheroma is present in most young adults, yet clinical coronary disease is uncommon under the age of 40 and, although it could be argued that coronary atheroma needs time to cause clinical features, advanced atheroma is often unassociated with myocardial infarction and conversely.

	Clinical coronary disease	Actual coronary atheroma
Increasing incidence	Yes	?
Sex difference	Yes	No
Frequent occurrence in early adult life	No	Yes

In other species myocardial infarction is rare in association with advanced coronary atheroma.

	Myocardial fibrosis or infarction	Actual coronary atheroma
Spontaneous occurrence in animals and birds	No	Yes
Experimental production in animals and birds	No	Yes

This attempt to distinguish between the clinical manifestations of coronary atheroma and the pathological lesions may be artificial but it serves to emphasize that their ætiology need not always be identical.

Since coronary atheroma may not be increasing in step with its clinical manifestations, some of the possible causes (apart from improved diagnosis) for the increasing incidence of clinical coronary disease were considered.

First, the incidence of thrombosis might be increasing. There is no sound evidence in support of this and, since fibrin and thrombi can be incorporated into the arterial wall to form atheromatous lesions, it might be expected that any increase in the incidence of thrombi would be reflected by an increase in atheroma. Moreover, pathologists maintain that no more than half the patients who die from a myocardial infarct have a preceding causal coronary thrombosis.

Second, there might now be a greater or more prevalent disturbance of cholesterol metabolism when compared with the beginning of the century. This might lead to impairment of the nutrition and function of the arterial wall without necessarily resulting in gross coronary atheroma. In general, the higher standard of living has resulted in greater energy intake and less energy expenditure, and this may have led to a disturbance of lipid metabolism in some subjects. Moreover, elaborate epidemiological and racial surveys have shown that, with some exceptions, the consumption of fat is closely related to the social and geographic incidence of hypercholesterolæmia and of clinical coronary disease. The plasma cholesterol, the plasma-cholesterol/phospholipid ratio, and the α/β lipoprotein ratio were analysed in 240 patients with electrocardiographic evidence of myocardial infarction under the age of 50 and in a comparable control group. With the selection of certain values as representing the upper limits of normality, it was found that 8 per cent of the coronary group and 93 per cent of the control group had entirely normal values; this arbitrary separation was not possible in older age groups. The ætiology of clinical coronary disease in young patients may, therefore, be more closely related to a disorder of lipid metabolism than in older patients. There may be two major types of coronary disease—one associated with an active metabolic disorder and another with advancing age.

Third, the remarkable social and economic changes of this century are undoubtedly stressful to some people, particularly if they have inherited an ambitious and conscientious personality. In Scotland the incidence of clinical coronary disease is greatest in executive, professional, business, and intellectual occupations, where the fat consumption is high and there are heavy responsibilities demanding prolonged and exacting mental strain. Such increasing stress might favour the development of clinical coronary disease by disturbing normal endocrine balance, and thus influencing both cholesterol metabolism and the

coagulation and fibrinolytic systems. Similarly, long continued environmental stress might disturb the autonomic control of the coronary arteries and thus upset the balance between the supply and demands of the myocardium.

In summary, there are certain differences in the prevalence of the clinical manifestations of coronary disease and in the prevalence of coronary atheroma and the former may not always be a simple product of the latter. There is indirect evidence to suggest that there might have been a greater and more widespread disturbance of lipid metabolism during this century. The circulating lipids and lipoproteins are frequently abnormal in young patients with clinical coronary disease and the ætiology in such patients may be closely associated with a disturbance of lipid metabolism. Environmental stress could disturb the balance between the supply and demands of the myocardium, and it may not be necessary, therefore, to postulate an increase in the incidence of coronary atheroma or of thrombosis to account for the increasing incidence of clinical coronary disease. Much further investigation is necessary for the elucidation of the complex ætiology of coronary disease.

Observations on the Morbid Anatomy of Coronary Artery Disease

By Prof. G. L. Montgomery (*introduced*), Edinburgh

Pathologists have long suspected that the incidence of thrombi in the coronary arteries in myocardial infarct is a function of the care with which the vessel is examined and of the method used. Ideally, segments of the artery should be cut in serial section for microscopy: practically, this is impossible. It has proved feasible, however, to harden the heart by deep-freezing, cut it on a mechanical slicer, and so obtain sections 2 mm. thick from base to apex. An adult heart provides roughly 50 transverse sections; in this way the coronary arteries can be examined from their ostia and portions taken for microscopic study.

The material consisted of 200 hearts, of which 108 were from cases with recent myocardial infarcts.

No occlusion and no thrombus	45 (42%)
Occlusion:	
(*a*) by soft atheroma—19 (*b*) by recent thrombus—17	36 (33·3%)
Non-occlusive recent thrombus	26 (24%)
Embolus	1 (0·7%)

"Non-occlusive recent thrombus" refers to partial thrombotic occlusion where, so far as could be ascertained, the appearances were not attributable to shrinkage: the significance of recent partial occlusion in relation to infarction is uncertain.

To account for myocardial infarction in the absence of coronary artery occlusion, the author drew attention to the over-all narrowing of the coronaries in his material. Gross stenosis of three major coronary arteries (i.e. both branches of the left together with the right) was found in 98 of his 108 cases: stenosis of two branches in 2, and of one branch only in 8 cases.

Attention was directed to the structure of the atheromatous plaques. The occurrence of concentric layering was compatible with Duguid's thrombotic theory; recent mural thrombus had been seen occasionally, but the means of incorporation of this material into the plaques remains unsolved from this study. Particular attention must be paid to soft atheroma as an occlusive material *per se*. Why does soft atheroma occur? What induces rupture of a plaque? The author found spicules of calcium in 20 per cent of his hearts, but gross calcification was not noted: as most of the patients were in the older age groups, the contrast with the London Hospital figures (quoted by Morris) is striking.

Microscopic examination of occlusive thrombi and of the infarcts emphasized the progressive nature of myocardial infarction and also that occasionally the occlusive thrombus appeared to be a terminal event in an established infarct. Obviously, this statement depends on whether the speed of organization of thombus in an atheromatous artery corresponds with that of thrombus in other situations. If this is so, and there is some evidence in support, it follows that in roughly half the 17 cases of thrombotic occlusion, the thrombus had developed within 24–28 hours of death, whereas the infarct had been present, sometimes painlessly, for longer.

Unequivocal evidence of hæmorrhages into an atheromatous plaque was found only in 5 per cent of the coronary arteries. It is difficult to be certain of hæmorrhages when a plaque has ruptured and fresh thrombus on its surface extends into the atheromatous material. In these instances thrombus and hæmorrhage are virtually inseparable histologically. Thus in this material, the relatively low incidence of hæmorrhage may be related with difficulty of interpretation or with the fact that most cases fall into older age groups. (See also Montgomery, G. L., *Scottish med. J.*, 1956, **1**, 367.)

Some Puzzling points concerning Coronary Artery Disease

By S. A. Levine, Boston, Mass.

Dr. Samuel Levine spoke about some puzzling points concerning coronary artery disease. He emphasized the lack of correlation sometimes between angina and the amount of effort required to produce it, and cited the well-known syndrome of second wind in anginal pain. He also questioned whether anti-thyroid treatment relieved angina solely by reducing the metabolic rate and pointed out that patients often improved symptomatically before their metabolic rate had fallen. In treating cardiac infarction he stressed the importance of getting patients out of bed to be nursed in a chair and stated that he believed that he had saved more lives in this way than by any other form of treatment.

This was followed by a discussion.

After lunch at Adam House the following Demonstrations were available.

Pathological findings in unusual cases of coronary artery disease. Prof. G. L. Montgomery (*introduced*).

The prognosis of untreated hypertension. F. O. Simpson (*introduced*).

Marfan's syndrome. R. J. G. Sinclair (*introduced*) and R. W. D. Turner.

The anatomy and relations of the heart. Prof. R. Walmsley (*introduced*).

Documented specimens of congenital heart disease. R. M. Marquis.

Angiocardiography. R. M. Marquis and D. R. Maitland (*introduced*).

Standard exercise studies during cardiac catheterization. M. B. Matthews.

The study of electrical activity of single cardiac tissue cells with intracellular electrodes. M. H. Draper (*introduced*).

Phonocardiography: the Gibson murmur and other continuous murmurs. J. D. Matthews (*introduced*).

Scientific Communications

Blood Coagulation in Patients with Ischæmic Heart Disease and Normal Subjects

By Lawson McDonald

Blood coagulation has been investigated in 50 patients with ischæmic heart disease, each of whom was matched with a normal subject of the same age and sex as a control. All patients had angina pectoris on exertion; in some there had been past cardiac infarction as well, but in none was this recent. Causes of cardiac pain other than coronary artery disease were excluded. Patients and controls were ambulant, and attended as out-patients for blood samples to be taken; conditions were standard with regard to time of day, activity, and food intake. The following tests were performed: prothrombin time, fibrinogen estimation, three different clotting times, estimation of factor VII (Owren) in plasma and serum, platelet count, estimation of platelet stickiness, and thromboplastin generation test.

A statistically significant difference was demonstrated between the patients and controls in respect of thromboplastin generation, platelet stickiness, fibrinogen estimation, and prothrombin time; it indicated an increased coagulability of the blood in the patients. This difference in blood coagulability between patients with ischæmic heart disease and normal subjects is discussed, with particular reference to the ætiology, natural history, and management of the disease.

Two Cases of Carcinoid Heart Disease

By J. Cosh

Two women, aged 67 and 65, were observed in hospital in the terminal stages of malignant carcinoid disease. The first had periodic facial flushing and diarrhœa for over two years before her death. She was admitted with congestive heart failure and died eight months later. The heart was much enlarged with a pulmonary systolic murmur; the liver was enlarged with a hard and irregular surface. Her face and chest were deep red in colour with generalized telangiectasia and an occasional brick-red flush in addition. She later became cachetic, deeply jaundiced, and mentally confused. The urine contained much 5-hydroxy-indole-acetic acid. The second patient presented with congestive heart failure eight months before death; physical signs were similar to those in the first patient, but she had a less deep colour with no flushing, and diarrhœa occurred first three months before she died.

Autopsy in each showed large metastatic deposits of carcinoid tissue in the liver and a small intestinal primary tumour. Tricuspid and pulmonary valve lesions were present and there were thick collagenous deposits on the endocardium of the right atrium and ventricle.

A Comparative Study of some Vectorcardiographic Techniques Using an Oscilloscopic Recorder

By A. J. V. Cameron and W. M. Lancaster (*introduced*)

With a specially designed instrument (the Cambridge Vectorcardiograph), three vector systems have been studied in healthy subjects and in certain types of cardiovascular disease. Basically the instrument consists of twin cathode ray oscilloscopes mounted side by side and fed by the outputs of three amplifiers. Two vector loops can then be displayed simultaneously. Central blurring of the loops is minimized by beam modulation. Interrupted time marking of the loops at various speeds is possible. The shape of the time marks indicates the direction of rotation of the loops. A camera is incorporated in the instrument and the loops can be photographed under visual control with the aid of a triggering device. Graduated amplification enables correction factors to be applied to any scalar component of the vectorcardiogram.

The lead connections and switching arrangements have been designed for versatility so that any reference frame may be used. The three frames studied have been (1) the unipolar system (using leads V2, V6, and aVF), (2) the equilateral tetrahedron system, and (3) the cuboid system. Electropositive polarity has been adopted and a scheme for analysis of the loops is suggested. The general features of the normal vectorcardiogram are fairly similar in all three systems but there are some differences in detail. Discrepancies are more obvious in the abnormal tracings.

The unipolar system has practical advantages in ease of recording and correlation with the routine unipolar leads but is subject to certain theoretical objections particularly with regard to preferential proximity of its scalar components to the heart. The full equilateral tetrahedron system is too complex for clinical use, while its frontal and sagittal projections alone do not give a sufficiently comprehensive picture in many cases. The cuboid system is probably the method of choice at present although it has the disadvantage of using bipolar scalar components which are not related to the accepted unipolar electrocardiographic leads .

A Family Consisting of Three Cases of Hunter's Polydystrophy (Gargoylism) with Cardiac Lesions

By R. E. Steen

These three children have intelligence quotients of 114, 101, 134. Suggestive features are their rather large heads, somewhat flat faces, depressed nasal bridges, ears set low, flared thoracic borders, and genua valga. Unequivocal evidence is provided by the following features: (1) the typical corneal lesions, which however are only demonstrable by ophthalmoscopic examination; (2) the characteristic chondrodystrophy in the bones, seen best in X-rays of the spine; and (3) the cardiac lesions which all three show. The eldest has apical systolic and diastolic murmurs, and an aortic systolic murmur which sounds organic. The second has an aortic systolic murmur which also sounds organic. The third has a loud apical systolic murmur, and a similar, though less loud, aortic systolic murmur. These features are illustrated by slides showing photographs of the children, X-ray photographs of the bones, phonocardiograms, etc.

The interest of these cases, which are possibly more common than would appear, is that if one were not aware of the condition and able to recognize the minor suggestive stigmata, so as to leave no doubt after an ophthalmoscopic examination and an X-ray photograph of the bones, one might easily confuse these otherwise apparently normal children with cases of rheumatic heart disease.

Selective Cine-angiocardiography using Image Intensification

By C. Pickard (*introduced*) and H. Watson (*introduced*)

With image intensification it is possible to obtain cine-angiocardiograms at relatively high speeds. Using this method and a selective technique whereby opaque medium is injected into the right ventricle, serial images of its outflow tract and the pulmonary artery can be obtained throughout systole and diastole—thus distinguishing the normal infundibulum in various stages of contraction from infundibular stenosis. This information aids precision in diagnosis and is of value to the surgeon when planning his attack on the pulmonary or infundibular obstruction.

Amyl Nitrite in the Differentiation of Regurgitant and Ejection Systolic Murmurs

By John Barlow (*introduced*) and John Shillingford

The clinical differentiation of regurgitant and ejection systolic murmurs may in some patients present considerable difficulty. Theoretically amyl nitrite by lowering the peripheral resistance in the systemic

arterial system should decrease the backflow through an incompetent mitral valve, and by increasing the cardiac output should increase the flow through the aortic and pulmonary valves. This theoretical basis has been used in practice by noting the effect of amyl nitrite in a series of patients with mitral and/or aortic valve disease. In the former, inhalation of amyl nitrite reduces or abolishes the systolic murmur and in the latter group considerably increases the intensity of the murmur. Phonocardiographic studies confirm this, and the value of this simple test in clinical practice is discussed.

The Society dined at 7.45 p.m. in the historic buildings of the Royal College of Physicians, Edinburgh, the scene of the first dinner of the reconstituted Society in 1937.

Special Meeting with Harvey Tercentenary Congress

A Special Open Meeting of the British Cardiac Society was held as a part of the Harvey Tercentenary Congress at the Royal College of Surgeons, London, on Thursday, June 6, 1957. The President, Maurice Campbell, took the Chair at 9.30 a.m.; 78 members were present and the meeting was also attended by distinguished visitors from among the members of the Harvey Tercentenary Congress.

Scientific Communications

Vectorcardiography in Myocardial Infarction

By T. D. V. Lawrie and G. Howitt (*introduced*)

Standard limb lead and multiple chest lead electrocardiography often afford considerable information in the diagnosis of myocardial infarction. Some cardiologists believe that they are of limited value, in that they record changes as they affect a single plane and suggest that they should be replaced or supplemented by vectorcardiography which can give some indication of the summation effect of cardiac electrical forces as recorded on several planes.

Up to date, there is no general agreement as to what constitutes the best system for recording vectorcardiograms nor is there any clear indication of the advantages or disadvantages of the various systems that are in current use in the study of myocardial infarction.

Fifty patients who have had recent myocardial infarcts have been investigated by standard limb and unipolar electrocardiography and by vectorcardiography using the cube system. A further twenty patients have had additional investigations by tetrahedron and Milovanovich systems of vectorcardiography. Two instruments have been used—the Cambridge Vectorcardiograph and the Sanborn Portable Vectorcardiograph.

The relative merits and defects of electrocardiography and vectorcardiography are discussed and an attempt is made to compare the results obtained from the three systems of vectorcardiography.

The Influence of Ventricular Hypertrophy upon the Cardiogram of Cardiac Infarction

By J. F. Goodwin

The causes of an rS complex in lead V5 were investigated in a study of 85 autopsied cases that had a predominently negative deflection in V5. Thirty-one had right ventricular hypertrophy only, 20 combined ventricular hypertrophy, 26 cardiac infarction and hypertrophy of one or both ventricles, and 8 infarction without ventricular hypertrophy.

Of the 34 cases with infarction, 25 had anteroseptal or pure anterior infarction. Fifteen cases had classical cardiographic signs of anterior infarction; 15 showed an rS pattern in lead V5 suggestive of extreme clockwise rotation due to right ventricular hypertrophy; and 4 showed an equivocal pattern suggestive, but not diagnostic, of infarction. The classical signs of infarction were more common when ventricular hypertrophy was absent than when it accompanied infarction, when the rS pattern was often found.

When there was an rS pattern in V5 in the presence of infarction, the heart was usually horizontal or intermediate in position, the P waves were normal, the R/S ratio less than 1 in V4R or V1, and the T waves usually inverted in V5 and positive in V4R or V1. Augmented, pointed, P waves, a vertical heart position,

and T wave negativity in V4R or V1 with positivity in V5, suggested right or combined ventricular hypertrophy without infarction, but in many cases infarction could not be diagnosed or excluded with certainty.

The genesis of the rS complex in V5, and the influence of ventricular hypertrophy upon the diagnostic pattern of infarction are discussed.

Observations on the Mechanism of the Hypertension in Coarctation of the Aorta

By J. F. Pantridge, G. C. Patterson (*introduced*), J. T. Shepherd and R. F. Whelan (*introduced*)

The peripheral circulation has been studied in 9 patients with coarctation, 6 women and 3 men, aged 20–34 years. The blood flow through the forearm and calf was measured by venous occlusion plethysmography and the brachial and femoral pressures by electromanometry. The resistances to flow through the limb segments were calculated and the results compared with those obtained in 9 normal subjects of similar age and sex. The resistances were studied both under resting conditions and with the vessels dilated by local heating. Under both conditions, the resistance to flow through the upper limb was increased in the patients while that through the calf was within normal limits.

The results do not support the concept of a humoral or neurogenic mechanism as the cause of the hypertension, since either of these would be expected to increase the resistance to flow both above and below the coarctation. They would be consistent with the concept that the hypertension is initiated by the resistance of the coarcted segment and the collaterals, and augmented by the local increase in vascular tone of the upper limb vessels which can occur in response to a rise in intravascular pressure.

Hypertonia or Uneventful High Blood Pressure

By William Evans

To be published in full in the Lancet

The Electrocardiogram in Aortic Stenosis

By Peter Fleming (*introduced*) and Ronald Gibson

An analysis has been made of a series of electrocardiograms of 50 patients with aortic valve disease who have been investigated by the technique of percutaneous left ventricular puncture. The main purpose of the study was to determine the precision with which the severity of aortic stenosis can be assessed from the electrocardiogram. The systolic gradient across the aortic valve has been used as an absolute criterion of severity against which electrocardiographic changes could be measured. The reasons for the choice of this criterion are given. Cases with lesions such as ischæmic heart disease that could have influenced the electrocardiogram have been omitted from the analysis, but cases with concomitant mitral stenosis have not been excluded.

In cases of pure or dominant aortic stenosis, the magnitude of the left ventricular potential in chest and unipolar limb leads correlated well with the systolic gradient and in such cases the gradient can be predicted with fair accuracy from the electrocardiographic changes. RS–T and T wave changes gave similar but less precise information. A normal electrocardiogram was always associated with, at most, an insignificant systolic gradient across the aortic valve.

In cases with significant aortic regurgitation, the electrocardiographic changes were more severe than would have been expected from the systolic gradient. Measurement of the gradient and comparison with the electrocardiogram is a useful method of assessing the degree of aortic regurgitation.

The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy in Infancy and Childhood

By Arthur Hollman

Criteria have been designed, from data from normal electrocardiograms, to distinguish between physiological and pathological degrees of right ventricular hypertrophy in infancy and childhood. In order to test the validity of these criteria the electrocardiograms of 29 cases of congenital heart disease with autopsy proof of lone right ventricular hypertrophy were analysed. By use of the criteria it was possible to diagnose right ventricular hypertrophy in 93 per cent of the cases, over half of whom were under the age of one year. In general the ratio or algebraic sum of the R and S waves in leads V1 and V5 were found to be the most useful criteria. In lead V1 under the age of four months the algebraic sum of R and S is more reliable than the ratio. An abnormally low ratio of R to S in V5 may be used as reliable evidence of right ventricular hypertrophy in the absence of diagnostic changes in the other leads.

The Effects of Squatting in Patients with Cyanotic Congenital Heart Disease

By L. Brotmacher (*introduced*)

The effects of squatting have been investigated with special reference to the benefits obtained by patients with cyanotic congenital heart disease when they adopt this position.

Squatting produces kinking of the femoral and popliteal arteries and veins in the groins and popliteal fossæ. The arterial pressure in the legs is lowered, the venous pressure rises and, as a result, the blood flow in the legs is reduced. The overall systemic blood flow is increased by squatting, the rise in blood flow being especially great in the upper part of the body as a result of diversion of blood from the legs. There is no concomitant increase in tissue oxygen requirements: the arteriovenous difference lessens and the oxygen content of venous blood from the upper half of the body becomes greater, i.e. the anoxia is lessened in the part of the body that is most sensitive to oxygen lack. This is considered to be the basis of the benefits obtained by severely ill patients who squat independently of exertion.

Most forms of exertion involve the leg muscles. When patients with a veno-arterial shunt exercise, greatly desaturated blood from the legs reaches the right side of the heart and is shunted into the systemic arteries, producing a precipitous fall in arterial oxygen content. Squatting impedes the venous return from the legs and thereby reduces the contribution of desaturated blood from the contracting muscles to the mixed venous blood and to the shunt stream. Consequently, when a patient squats during recovery from exertion the arterial oxygen saturation returns to the resting level much more rapidly than when he stands. The resulting reduction in tissue anoxia is thought to be the basis of the additional benefits obtained by squatting after exercise.

Some Aspects of Atrial Septal Defect

By D. Evan Bedford

During the last year, 100 cases of atrial septal defect have been investigated and 41 have been operated on by Mr. Holmes Sellors at the Middlesex Hospital by open heart surgery under hypothermia. There has been no mortality in closing the defect, but one patient died from a second operation to restore the inferior vena cava to the right atrium.

All patients submitted to surgery had fossa ovalis (ostium secundum) defects. In some, however, the septal aperture extended down to the inferior vena caval orifice which thus opened into both atria; and in such cases suturing the margins of the defect together may exclude the vena cava from the right atrium. High defects underlying the superior vena cava, and associated with anomalous right upper pulmonary veins, had been recognized in three cases by a localized dilatation of the lower end of the vena cava or by catheterization.

Atrio-ventricular (ostium primum) defects had been diagnosed in 13 cases, and none had been submitted to surgery. This type of defect could be suspected on the following grounds: (1) unusual cardiac enlargement or pulmonary hypertension in childhood, (2) left axis deviation in the electrocardiogram, (3) a pansystolic murmur at the apex or left sternal edge, sometimes with a thrill, and (4) a shunt at atrial *and* ventricular levels, or mainly at ventricular level.

Obstructive pulmonary hypertension (pulmonary systolic pressure over 50 mm. Hg and raised vascular resistance) occurred in 15 cases. Surgical closure of the defect was contraindicated in these cases, even if the shunt was still from left to right, if the vascular resistance was high; but when pulmonary hypertension was due to a large flow, a slightly raised resistance was no contraindication to surgery.

Mitral stenosis was diagnosed in only six cases, five of which had auricular fibrillation; and in three of them the diagnosis was confirmed by operation. Provided a mitral valvotomy was done at the same time, surgical closure of the atrial septal defect proved most beneficial.

The Electrocardiogram and Serum Lipids of Middle-aged Men without Cardiac Symptoms

By David Weitzman and Elspeth Smith (*introduced*)

Electrocardiograms at rest and after effort were recorded in 100 men aged 50 or over, and their serum lipoproteins were studied by paper electrophoresis. Subjects were selected on the following criteria: no chest pain (nor any history thereof), no valvular lesion, diastolic pressure less than 100 mm. Hg, no cardiac enlargement on X-ray, no evidence of diabetes or syphilis or renal disease, and no hypercholesterolæmia. They were divided into two groups according to the presence or absence of systemic arterial disease.

Unequivocally ischæmic electrocardiograms were obtained in 10 per cent of the men without peripheral

arteriosclerosis, and in 33 per cent of those with claudication or cerebral occlusion. All save one of the ischæmic tracings were abnormal at rest; the exercise test proved of little value in the detection of latent ischæmia. Abnormal lipoproteins were present in 73 per cent. Their extent and density bore no relation to electrocardiographic findings. The lipid patterns found in this series showed no consistent differences from those of patients with cardiac infarction.

A Pædiatric View of the Prognosis of Congenital Heart Disease

By R. E. Bonham-Carter and D. Waterston

The paper was divided into three parts. The first, which was a series of 200 necropsies from 1946 to 1956, showed that of the children who died, two-thirds did so under the age of six months and only one-sixth after the age of two years.

The second part showed the prognosis of acute cardiac illness in 217 consecutive cases of congenital heart disease between 1947 and 1953: within this group there were 90 under the age of one of whom 73 per cent died. The third part dealt with the period 1953 to 1956 inclusive and in this there were 141 cases of acute cardiac illness under the age of one, of whom 57 per cent died. In each of the three groups a distinction was made between potentially operable and inoperable lesions and it was shown that there had been some improvement from surgical influence in the last group: 46 per cent of those who were operable were operated upon, with a 46 per cent mortality rate. This was achieved largely by extra-cardiac surgery.

Circulatory Changes in Constrictive Pericarditis

By Frederic Jackson

Cardiac catheterization was performed in 12 cases of constrictive pericarditis, and repeated after operation in six of eight treated surgically. The resting cardiac output determined by the Fick principle was found in severe cases to be about half the normal, and the stroke volume less than half. After operation both output and stroke volume returned to near normal. Oxygen consumption at rest altered little before and after operation, but the arterio-venous oxygen difference halved after operation in conformity with the restoration of the cardiac output.

The mean right atrial pressure and the right ventricular diastolic filling pressure were high in every case and fell greatly after removal of the constriction, while the pulse pressure in the right ventricle, small before operation, increased in amplitude afterwards. The mean pulmonary artery pressure was commonly a little raised, though the gradient over the pulmonary valve was abnormally small and increased after operation. The mean pulmonary capillary pressure was also raised and was always higher than the pressure in the right atrium, suggesting that the " constriction " hampers the filling of the left ventricle as well as the right. At every site the pressures were lower in cases re-catheterized after operation. Some implications of these findings are discussed with their bearing on the selection of cases for surgery.

Dye Dilution Curves in the Clinical Assessment of Mitral Valve Disease

By John Shillingford and Max Zoob

We have shown previously that the regurgitant flow through an incompetent valve could be estimated from a dye dilution curve together with the cardiac output and intrathoracic volume. A clinical, surgical, and pathological study on a series of patients with mitral valve disease has been made by one of us (M.Z.) and an estimation of the degree of valvular insufficiency divided into one of four groups according to its severity. Estimations of regurgitant flow have been made independently on the same patients by a different observer (J.S.) and the cases divided into four groups according to the volume of flow. The results were then compared and found in most cases to give close agreement. The limits of accuracy and practical value of this test in assessing patients before surgery are discussed.

Cerebral Blood Flow in Mitral Stenosis and its Response to Carbon Dioxide Inhalation

By H. A. Dewar and L. A. G. Davidson (*introduced*)

In an attempt to establish the possible value of inhalation of carbon dioxide as a method of treatment for cerebral embolism, the cerebral blood flow of a number of patients suffering from mitral stenosis was measured by the nitrous oxide method before and after inhalation of a 5 per cent concentration of CO_2 in air. The increase in cerebral blood flow was less than normal but still significant. There was a rough

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inverse relationship between the extent of the increase and the severity of the valve defect. The opportunity was taken to compare the cerebral blood flow of this and another series of cases of mitral disease with normal subjects; it was found that in the mitral cases the cerebral blood flow was low but the oxygen uptake was normal unless morphine had been given when the oxygen uptake also was decreased.

The Third World Congress of Cardiology

This will be held at Brussels from September 14 to 21, 1958. Members of the British Cardiac Society should have received the preliminary booklet, but if not and they wish to attend they should write to the Secretariat, 80, Rue Mercelis, Brussels, Belgium.

Members wishing to give communications should submit an abstract of not more than 200 words to the Secretary, British Cardiac Society. Two typed copies (in double line spacing) must be submitted in English, *and* in French or German or Spanish at the author's choice, before February 1, 1958.

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